Major pathological response after neoadjuvant immunotherapy in esophageal spindle cell carcinoma: A case report

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Abstract
Esophageal spindle cell carcinoma (ESpCC) is a rare subtype of esophageal carcinoma, accounting for 1% of all esophageal malignancies. The clinical outcome is unknown due to the lack of treatment options. Here, we present the case of a 60-year-old male with initially unresectable ESpCC, in which platinum-based concurrent chemoradiotherapy was unsuccessful. He was subsequently treated with neoadjuvant immunotherapy and after surgery achieved a complete pathological response; therefore, neoadjuvant immunotherapy might be a novel option for ESpCC patients.

KEYWORDS
esophageal spindle cell carcinoma, immunotherapy, neoadjuvant treatment

INTRODUCTION
Esophageal cancer is one of the most common gastrointestinal malignancies, affecting millions of people worldwide.1 Esophageal spindle cell carcinoma (ESpCC) is a rare subtype (about 1%), consisting of a mixture of spindle cells and squamous cells of the same origin.2–4 ESpCC occurs commonly in males between age of 60–70 years, typically presenting as an intraluminal polypoid mass in the middle of the esophagus.4–6 The most common symptoms are dysphagia and weight loss, followed by pain.7–16

Optimal treatment of this rare disease is unclear, and it is often treated as poorly differentiated squamous cell carcinoma. Partial or total esophagectomy and lymph node dissection are usually adopted.4 For locally advanced esophageal cancer, neoadjuvant chemoradiotherapy brings longer event-free survival and overall survival.8–11 However, this modality remains highly questionable for ESpCC. Few patients have been treated with neoadjuvant or adjuvant therapy in previous studies. Here, we report a patient with locally advanced ESpCC in which treatment with neoadjuvant concurrent chemoradiotherapy failed. He was subsequently treated with neoadjuvant immunotherapy and after surgery achieved a complete pathological response.

Neoadjuvant immunotherapy might therefore be a novel option for ESpCC patients.

CASE REPORT
A 60-year-old male came to our hospital with a chief complaint of dysphagia and chest pain for a month. Nodular changes located 23–30 cm from the incisor were visualized by upper endoscopy, involving the whole circumference of the esophageal wall. ESpCC was established by pathological examination, and confirmed by IHC staining (Figure 1) which indicated p63 (+), CK5 / 6 (+), p53 (+), PCK (+), SMA (−), S-100 (−), desmin (−), and Ki-67 (80%). PD-L1 expression was evaluated using the IHC 22C3 pharmDx assay, and a combined positive sore of 40 was assessed. His tumor was judged to be locally advanced (cT3N1M0) through our diagnostic work-up consisting of brain magnetic resonance imaging (MRI), chest and upper abdominal enhanced computed tomography (CT), and bone scintigraphy.

Neoadjuvant chemoradiotherapy was prescribed after consultation with our multidisciplinary team. The chemotherapy regimen consisted nab-paclitaxel plus nedaplatin combination. The dose of thoracic radiotherapy was 4320 cGy/24 F. However, the therapy achieved no efficacy and his tumor remained intact. After discussion, we changed the original...
scheme, and sintilimab (an anti-PD1 antibody, Innovis Inc) at a dose of 200 mg combined with nab-paclitaxel was given every three weeks for two cycles. The lesion markedly decreased in size, and his dysphagia was alleviated (Figure 2).

He finally underwent resection and lymph node dissection of esophageal carcinoma.

Postoperative pathological examination revealed only a few residual tumor cells in the resected tumor sample, with

**FIGURE 1** Pathological examination showed spindle cell morphology (A: H&E). (B–I) Immunohistochemistry data: CK5/6 (+), P63 (+), PCK (+), SMA (−), desmin (−), s-100(−), ki-67 (+, positive proportion about 80%) and PD-L1(+, positive proportion about 40%), supported the diagnosis. (J) Few tumor cells remained in the postoperative pathological sample. Original magnification, (A–H,J) × 400 and (l) × 200

**FIGURE 2** Summary of radiological evaluation
| Trial                                             | Phase | Intervention Population          | Patients | Therapy                                                                 | Primary outcome                  | Status          |
|--------------------------------------------------|-------|---------------------------------|----------|--------------------------------------------------------------------------|----------------------------------|-----------------|
| NCT04437212                                      | 2     | Single Group LA-ESCC            | 20       | Paclitaxel/cisplatin + RT + toripalimab + pembrolizumab                  | MPR                              | Recruiting      |
| NCT02998268                                      | 2     | Parallel LA-EAC                 | 46       | Pembrolizumab + paclitaxin + carboplatin + surgery                       | DFS                              | Active          |
| NCT03064490                                      | 2     | Single Group LA-ESCC            | 18       | Pembrolizumab + paclitaxin + carboplatin + surgery                       | DFS                              | Recruiting      |
| NCT03792347                                      | 1b    | Single Group LA-ESCC            | 20       | Carboplatin/paclitaxel + RT + pembrolizumab                              | Safety                           | Recruiting      |
| NCT02844075                                      | 2     | Single Group LA-ESCC            | 25       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Active          |
| NCT02998268                                      | 2     | Parallel LA-EAC                 | 36       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |
| NCT03044613                                      | 1b    | Single Group II/III Gastro/esophageal cancer | 25   | Nivolumab + C6 + relaitimab, carboplatin + paclitaxel + RT                  | Safety                           | Recruiting      |
| NCT03914443                                      | 2     | Single Group LA-ESCC            | 36       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |
| NCT03949413                                      | 2     | Single Group Resectable ESCC     | 20       | Toripalimab + paclitaxin + carboplatin + RT                              | DFS                              | Recruiting      |
| NCT03946969                                      | 2     | Single Group LA-ESCC            | 25       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |
| NCT04212598                                      | 2     | Single Group LA-ESCC            | 20       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |
| NCT03087864                                      | 2     | Single Group II/III esophageal cancer | 20   | Atezolizumab + carboplatin + paclitaxin + RT                               | Safety                           | Completed       |
| NCT03448835                                      | 2     | Single Group Resectable EAC      | 20       | Durvalumab + paclitaxin + carboplatin + RT                               | DFS                              | Recruiting      |
| NCT04177875                                      | 2     | Single Group LA-EC              | 44       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |
| NCT04320822                                      | 2     | Single Group EAC/EGJ AC          | 40       | Atezolizumab + carboplatin + paclitaxin + RT + S-1                      | pCR                              | Recruiting      |
| NCT04548440                                      | 2     | Single Group LA-EC              | 44       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |
| NCT03940001                                      | 1     | Single Group LA-ESCC            | 20       | Pembrolizumab + paclitaxin + carboplatin + RT + S-1                      | pCR                              | Recruiting      |

Abbreviations: CF, 5-FU; CDDP, Cisplatin; DCF, 5-FU, CDDP, DTX; DFS, disease-free survival rate; EAC, esophageal adenocarcinoma; EGI AC, esophagogastric junction adenocarcinoma; ESCC, esophageal squamous cell cancer; LA-EAC, locally advanced esophageal adenocarcinoma; LA-ESCC, locally advanced esophageal squamous cell cancer; MPR, major pathological response; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse events.
scattered lymphocyte infiltration. All the 18 excised lymph nodes were free of tumor cells (ypT1N0M0).

He was maintained on adjuvant sintilimab therapy for another two cycles. Unfortunately, he had gradual onset of exertional dyspnea, and chest CT showed inflammatory infiltration, interstitial involvement, and partial consolidation in bilateral lungs. Immune-related pneumonitis was suspected. After intense methylprednisolone (3 mg/kg) and low dose cyclophosphamide (500 mg every week) therapy, the lung lesions gradually resolved. He has survived for 12 months at the time of writing this report.

DISCUSSION

ESpCC has been classified as a special subtype of esophageal squamous cell carcinoma by WHO in 2010.12 The pathogenesis of ESpCC remains elusive. It is considered to be either a mixed tumor of spindle and squamous cancer cells from a common origin, or a collision of these two kinds of malignant cells from different origins.2, 7 ESpCC exhibits strong immunostaining with cytokeratin AE1/AE3, both in epithelial and spindle compartments. Strong vimentin staining has also been observed in spindle tumor cells. The transitional areas between spindle cell and carcinomatous cells have been previously reported to be positive for both cytokeratin and vimentin.2, 13–15 The prognosis of ESpCC may be better than that of squamous cell carcinoma. This might be due to its tendency of intraluminal occurrence, and early onset of symptoms.4, 16

Our patient received neoadjuvant chemoradiotherapy, which has been shown to improve the prognosis of ESCC. Previously, only one case of ESpCC treated with neoadjuvant therapy has been reported. Neoadjuvant radiotherapy was reported to have an extraordinary objective response in the patient in that study who died after 14 months.17 Our patient received concurrent chemoradiotherapy as an initial treatment, without noticeable change in tumor size. However, the tumor significantly decreased in size after immunotherapy. Few residual tumor cells were found in postoperative pathology. The treatment process strongly supports the efficacy of immunotherapy in this type of esophageal cancer.

Immunotherapy, including immune checkpoint inhibitors (ICIs), has changed the treatment landscape of esophageal cancer. At least three phase III trials (KEYNOTE-181 for pembrolizumab, ATTRACTION-3 for nivolumab, and ESCORT for camrelizumab) have confirmed the superiority of immunotherapy over chemotherapy in second-line esophageal cancer therapy.18–20 In a phase III KEYNOTE-590 study, pembrolizumab combined with 5-FU and cisplatin significantly improved OS and PFS in first-line therapy.21 Perioperative immunotherapy is under active exploration. Checkmate-577 proved the efficacy of adjuvant nivolumab for patients undergoing concurrent chemoradiotherapy for neoadjuvant.22 A dozen neoadjuvant immunotherapy clinical trials are ongoing (Table 1).

ESpCC is also referred to as esophageal sarcomatoid carcinoma (SC). Studies in SC of other sites might lend meaningful references to the largely-unknown treatment of ESpCC. SC is usually an extremely malignant tumor with a poor outcome which has previously been reported to be resistant to chemotherapy or radiotherapy.23 Yvorel et al. measured PD-L1 (defined as >10%) that was expressed in 75% (27/36) of pulmonary SC patients.24 In another report, a PD-L1 expression rate of 53% (40/75) in pulmonary SC patients was reported, higher than other subtypes of NSCLC.25 High expression rates of PD-L1 in kidney SC have also been observed.26, 27 High tumor mutation burden (TMB) has been reported to be more common in pulmonary SC than other types of NSCLC. In the report by Alexa et al., where high TMB was defined as >20/Mb, the proportions of high TMB were 20% and 14%, respectively.28 In another report, high TMB (>10/Mb) was observed in 87.5% (7/8) of PSC patients.29 In addition, at least one article has reported the high density of CD8+ tumor infiltrating lymphocytes in the microenvironment of sarcomatoid renal cell carcinoma (SRCC).30 It is generally believed the expression of PD-L1 and TMB are positively correlated with immunotherapy.24–26 Therefore, the prospect of PD-1/ PD-L1 inhibitors for the treatment of SC seems promising. This has been confirmed by retrospective studies and also anecdotal case reports on pulmonary SC and SRCC.31–33

Recently, the combination of durvalumab (an anti-PD-L1 antibody) plus tremelimumab (an anti-CTLA4 antibody) in the treatment of pulmonary SC was tested in a prospective single-arm phase 2 trial (KCSG-LU16-07). The results showed that PFS, OS, ORR and DCR were 5.9 m, 15.4 m, 26.7% and 60%, respectively.26 In four phase 3 trials (KEYNOTE-426, CheckMate-214, IMmotion151 and JAVELIN Renal 101), pembrolizumab, nivolumab, atezolizumab andavelumab were shown to bring survival benefit to SRCC in subgroup analyses.30, 37–40 All these studies suggest that there are potential benefits of immunotherapy for SC, which might be helpful in the treatment of ESpCC.

In conclusion, in this report we described a case of esophageal carcinosarcoma treated with neoadjuvant immunotherapy after failure of preoperative chemoradiotherapy. Immunotherapy might therefore be a useful candidate for patients with locally advanced ESpCC.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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