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Combination therapy with toripalimab and anlotinib in advanced esophageal squamous cell carcinoma: A case report

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Abstract

BACKGROUND

Toripalimab and anlotinib have shown good response in esophageal cancer, with high objective response rate and progression free survival. Thus, they have been approved as second-line or above-line therapy for advanced or unresectable esophageal carcinoma. Combination of these two drugs may have synergistic effects, but evidence of which is lacking.

CASE SUMMARY

Here, we report on a 73-year-old male, newly diagnosed with advanced esophageal squamous cell carcinoma (ESCC), who received a combination of toripalimab and anlotinib. Complete response was achieved after treatment for 3 mo and remission was maintained up to 14 mo.

CONCLUSION

The combination therapy of toripalimab and anlotinib is a promising treatment for unresectable ESCC and related clinical trials are warranted.

Key Words: Esophageal squamous cell carcinoma; Toripalimab; Anlotinib; Complete response; Case report

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Core Tip: Toripalimab and anlotinib have emerged as second-line or above-line treatment options for advanced esophageal cancer. However, their objective remission rates and progression-free survival are low when used alone. We report a case of complete response after combination therapy of toripalimab and anlotinib in a patient newly diagnosed with advanced esophageal squamous cell carcinoma. The patient was in remission for 14 mo. Hence, toripalimab combined with anlotinib may be a new and effective treatment for advanced unresectable esophageal squamous cell cancer.

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INTRODUCTION

Esophageal cancers are diagnosed at an advanced stage in several cases, and most patients with radical operations are prone to relapse and metastasis[1]. For unresectable, advanced, or metastatic esophageal cancer, platinum-based chemotherapy regimens have been recommended globally for decades. The median survival duration of patients on chemotherapy is less than 1 year[1]. Compared with the poor survival outcomes of chemotherapy, immune checkpoint inhibitors and tyrosine kinase inhibitors have shown promising result. These newer therapies are now being used widely and have resulted in longer overall survival, longer progression-free survival (PFS), and lasting objective response rates[2, 3].

Toripalimab exhibited remarkable anti-tumor activity in a variety of tumor types such as nasopharyngeal carcinoma, malignant melanoma, esophageal squamous cell carcinoma (ESCC), and other tumors by inhibiting the programmed cell death protein 1 (PD-1) /programmed death ligand-1 (PD-L1) pathway and, thus, promoting apoptosis[2]. Anlotinib is a new, oral, small molecule and multi-targeting tyrosine kinase inhibitor. It targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptors (PDGFR), thereby inhibiting tumor angiogenesis and cell proliferation[3].

The relevant studies on combined therapy with toripalimab and anlotinib in advanced ESCC are limited[4-6]. Here we report a patient newly diagnosed ESCC, who achieved complete response (CR) after 5 cycles of combination therapy with toripalimab and anlotinib and was in remission for up to 14 mo.

CASE PRESENTATION

Chief complaints

A 72-year-old man complaining of pain in the upper abdomen for a period of 1 mo was admitted to the hospital on February 11, 2022.

History of present illness

The clinical symptoms of vague upper abdominal pain started 1 mo ago with no apparent cause.

History of past illness

The patient was previously in good health.

Personal and family history

The patient had no personal or family history of cancer or liver diseases.

Physical examination

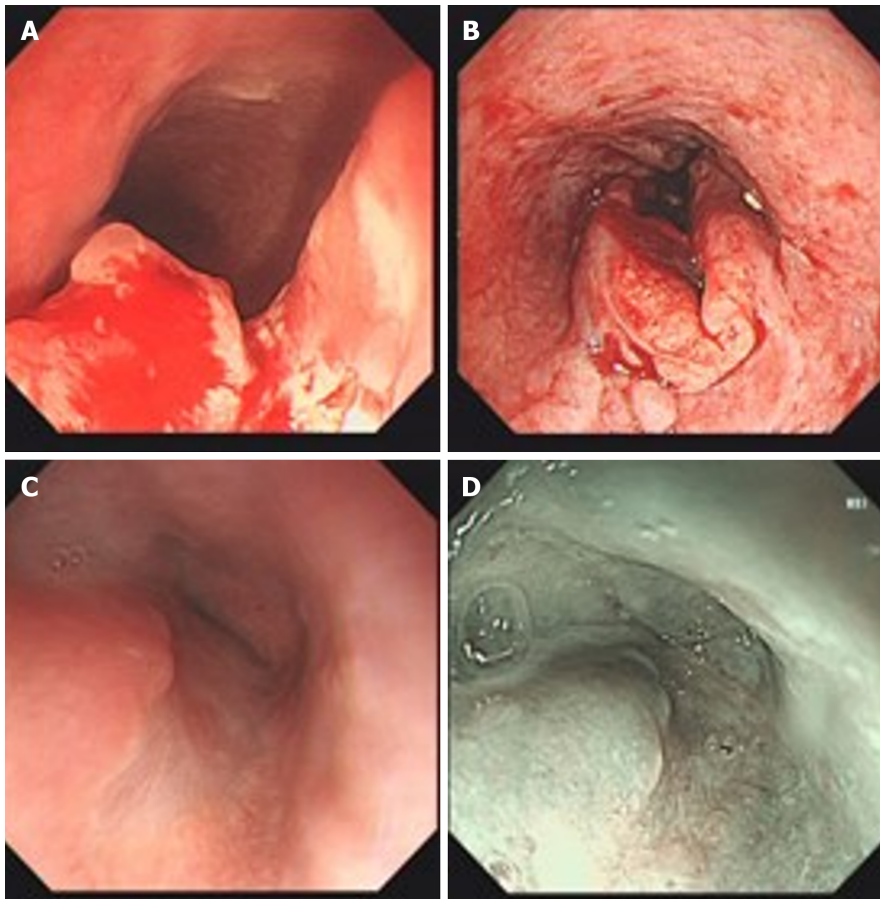
The abdomen was flat and tender, with no pressure or rebound pain throughout the abdomen. No abdominal masses were detected through palpation.

Laboratory examinations

Tumor markers suggested increased levels of cytokeratin-19-fragment (42.3 ng/mL), squamous cell carcinoma antigen (4.6 ng/mL), carbohydrate antigen 125 (168.3 U/mL), and carbohydrate antigen 199 (44.4 U/mL).

Imaging examinations

The gastroscopy showed a protruded lesion with an ulcer located at the middle and distal esophagus (Figure 1). Subsequently, the presence of infiltrative squamous cell carcinoma was confirmed through endoscopic biopsy (Figure 2). Positron emission tomography/computed tomography (CT) showed a 5.2 cm × 4.4 cm × 5.4 cm hypermetabolic mass located in the body of pancreas, and thickened middle and lower segments of the esophagus. Additionally, hyper-



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Figure 1 Results of endoscopy. A: The lesion located at the middle and lower parts of the esophagus before therapy; B: Image after endoscopic biopsy; C: Tumor shrank or disappeared after 3 mo of combined toripalimab and anlotinib therapy; D: Staining magnifying endoscope after 3 mo of the combination therapy.

metabolic and multiple lymph nodes were observed in the right mediastinum, hilum, surrounding pancreas, retroperitoneum, and the surrounding hepatogastric ligament (Figure 3).

FINAL DIAGNOSIS

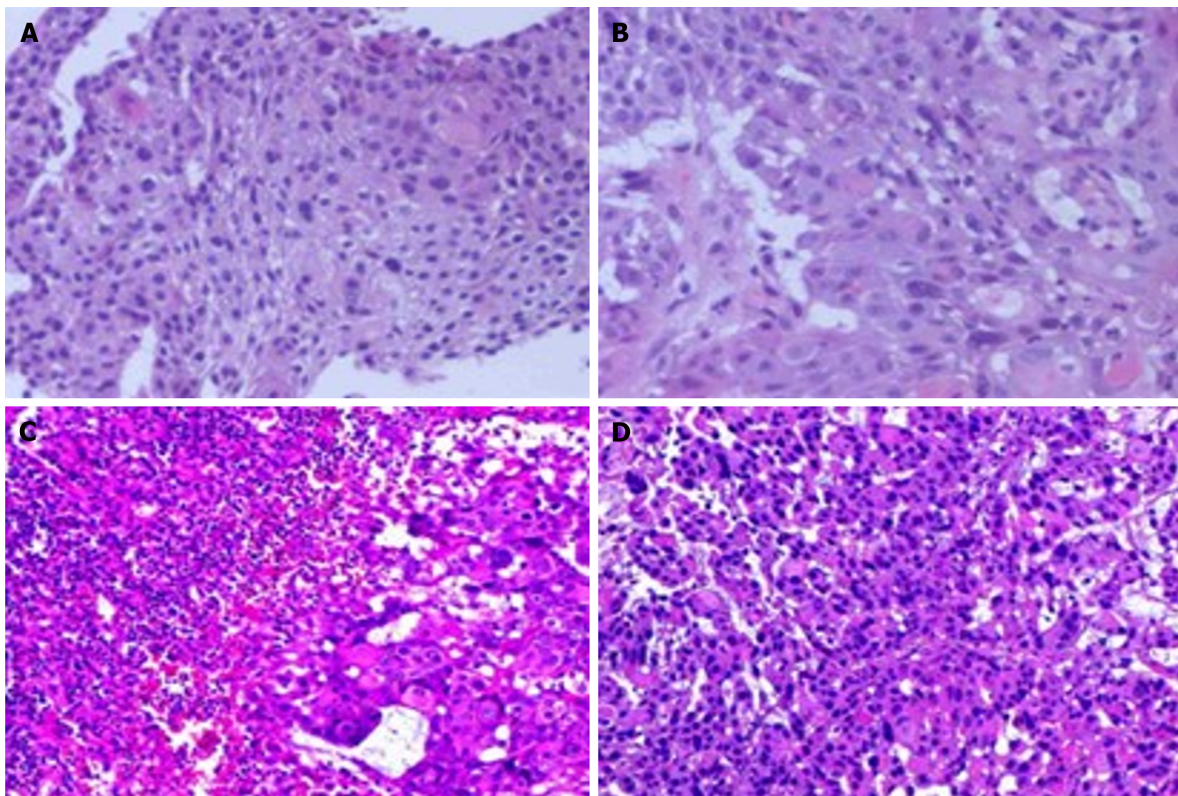
Laparoscopic biopsy was performed to identify the primary tumor and the combined pancreatic metastases. During the operation, a hardened texture was noted on the body of the pancreas, therefore, few lymph nodes near the common hepatic artery were resected and sent for pathological examination. The pathologic findings revealed lymphatic metastasis of esophageal carcinoma (Figure 2C and D). This patient was diagnosed with ESCC based on gastroscopy and pathological examination findings. Imaging findings suggested multiple lymph node metastases in the abdomen and distal areas. Consequently, he was diagnosed with advanced and unresectable ESCC.

TREATMENT

According to the patient's condition and wishes, he was administered toripalimab intravenously (240 mg administered on day 1 of every 3-wk cycle) combined with anlotinib orally (12 mg administered on days 1-14 of every 3-wk cycle) post-operatively.

OUTCOME AND FOLLOW-UP

Within 1 mo of starting the combination therapy, tumor markers decreased to normal levels and CT reexamination showed a shrinkage in tumor mass and lymph nodes (Figure 4A and B). After 3 mo of treatment, repeated endoscopy showed that the esophageal tumor had diminished or disappeared, and repeated CT also revealed the disappearance of the tumor and metastatic lymph nodes (Figure 4C and D). CR was achieved according to response evaluation criteria in



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Figure 2 Histopathological examination by hematoxylin-eosin staining. A and B: Heterogeneous proliferation of tissue squamous epithelium. The heterogeneous cells break through the basement membrane and infiltrate below the mesenchyme (40 ×, 200 ×); C and D: The squamous epithelial cells were markedly heterogeneous and showed infiltrative growth, and a little lymphoid tissue was seen in their periphery (40 ×, 200 ×).

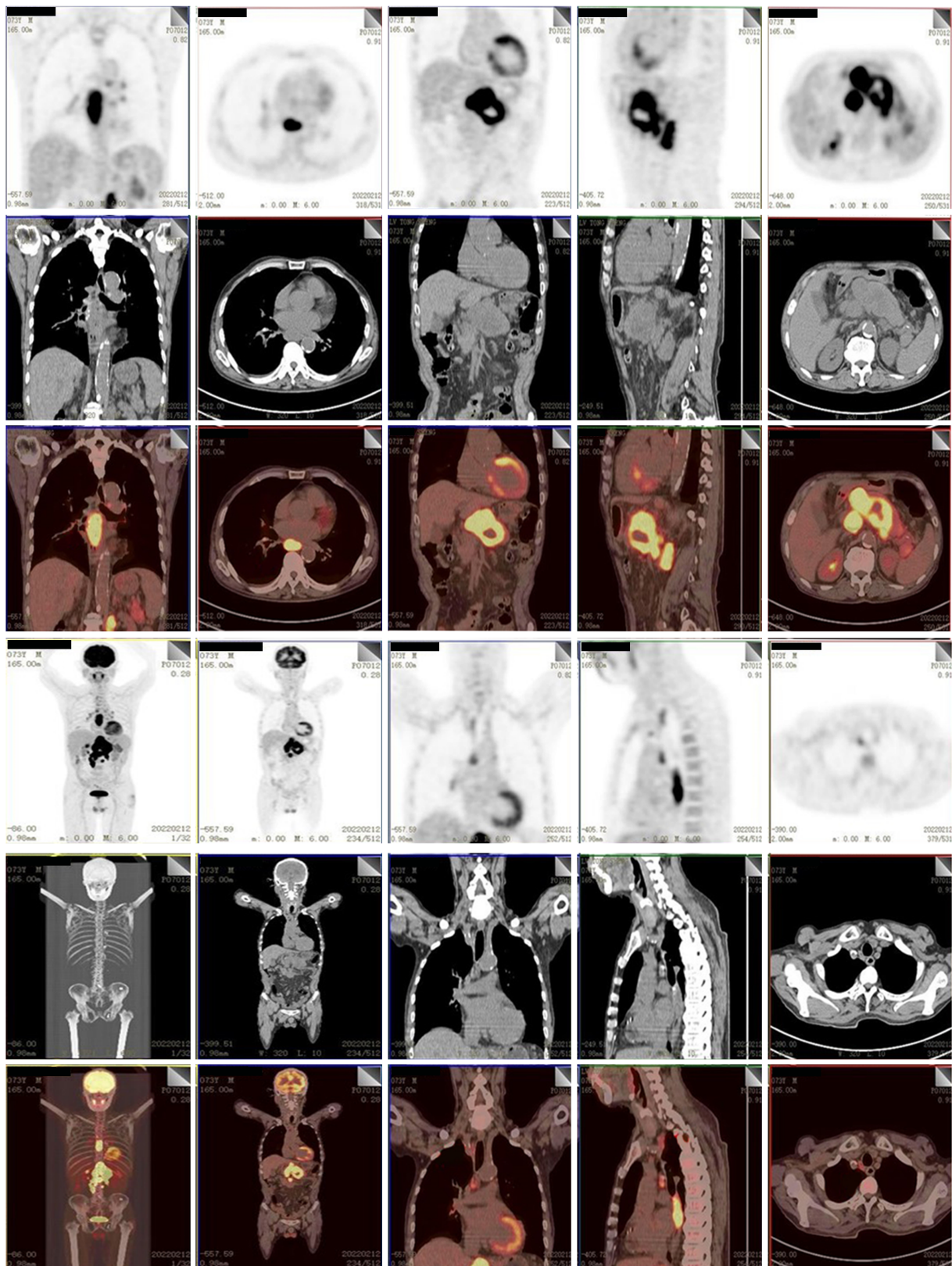
solid tumors criteria 1.1[7]. Based on CT reexamination, the patient was in remission for up to 14 mo since the initiation of combination therapy (Figure 4E and F).

DISCUSSION

PD-1, an inhibitory transmembrane protein, is widely expressed on T, B, natural killer, and myeloid-derived suppressor cells. By binding to its receptors PD-L1/L2, PD-1 can inhibit T cell activation or proliferation, which leads to tumor immune escape[8]. Nivolumab and pembrolizumab bind to the N-terminal loop and the C'D loop of PD-1 respectively [2]. Comparatively, toripalimab binds to the FG loop of PD-1 and blocks the PD-1 pathway, ultimately promoting apoptosis of tumor cells[2]. NCT02915432 concluded that toripalimab displayed potential anticancer activity with a manageable safety profile in chemotherapy drug resistant ESCC[9]. JUPITER-06, a double-blind and multicenter phase III clinical trial, involving 514 advanced ESCC patients revealed that compared to a simple chemotherapy (paclitaxel plus cisplatin) regimen, toripalimab combined with chemotherapy had higher overall response rate (ORR) (69.3% *vs.* 52.1%) and PFS (5.7 *vs.* 5.5 mo)[10]. The studies of NCT03985670[11] further support the synergistic effectiveness of toripalimab plus chemotherapy in the treatment of advanced esophageal cancer.

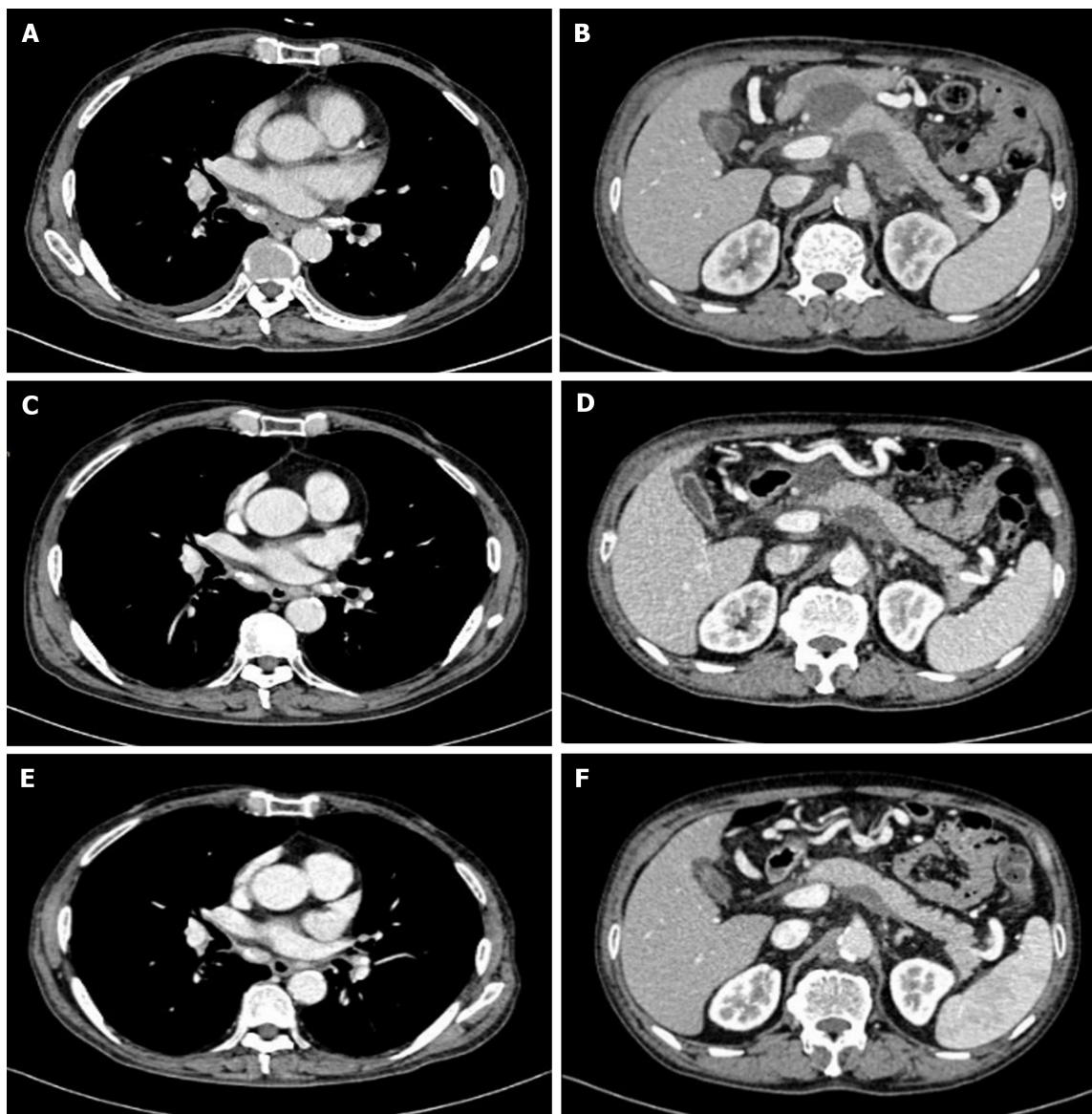
Anlotinib inhibits tumor angiogenesis and cancer cell proliferation by inhibiting VEGFR2, PDGFRβ, FGFR1, and downstream extracellular signal-regulated kinase signal transduction[3]. In a double-blind randomized phase II clinical trial (NCT02649361) involving 165 patients with recurrent or metastatic ESCC who were previously treated with chemotherapy, anlotinib was used to treat 110 patients, and the remaining 55 patients were given a placebo. The trial reported a prolonged PFS (3.02 *vs.* 1.41 mo) in patients who received anlotinib[12]. A multicenter, single-arm, phase II clinical trial (NCT04063683), involving 47 patients with previously untreated metastatic or unresectable locally advanced ESCC is currently underway, wherein anlotinib in combination with a chemotherapy regimen (paclitaxel and cisplatin) is being used for treatment. The preliminary results of this trial have shown a high ORR (74.1%) with the most significant adverse reactions being myelosuppression (18.5%) and hypertension (7.4%)[13]. These studies support the use of anlotinib as second-line treatment for advanced ESCC, either as monotherapy or in combination with chemotherapy.

Previous studies have demonstrated the potential synergistic anti-tumor effects of immunotherapy and targeted therapies, which were closely linked to the tumor microenvironment[14]. Intratumoral angiogenesis is essential for tumors to survive and grow. Dilated and fragile neovascularization predisposes the tumor tissue to hypoperfusion, thus leading to intratumoral hypoxia and acidosis[15]. Hypoxia and acidosis suppress anti-tumor immunity by the aggregation of immune suppressor cells (Treg and regulatory B cells) and by inhibiting the activation of immune effector



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Figure 3 Positron emission tomography/computed tomography scan images before the treatment. Two hypermetabolic shadows were respectively seen in each of the lower and middle esophagus (T6-9 level) and the body of the pancreas, which were diagnosed as malignancies. Multiple enlarged and hypermetabolic lymph nodes were located in the right mediastinum, hilum, surrounding pancreas, retroperitoneum, and the surrounding hepatogastric ligament.



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Figure 4 Enhanced computed tomography scan images during therapy. A and B: 1 mo after combined toripalimab and anlotinib therapy, the esophagus lesion and metastatic lymph nodes shrunk; C and D: The tumor and metastatic lymph nodes were disappeared after 3 mo of combination therapy; E and F: The tumor and metastatic lymph nodes have been disappeared for up to 14 mo since the initiation of combination therapy.

cells (activated CD8⁺ T and NK cells)[15]. In addition, increased vascular permeability and lymphatic drainage disorders increase the interstitial pressure around the tumor, which inhibits the delivery of drugs and immune effector cells to tumor[16]. The combination of amlotinib and teraplizumab exerted a synergistic anti-tumor effect. Anlotinib normalizes the tumor vasculature, upregulates the adhesion molecules in the tumor endothelium and induces a relatively immune-supportive tumor microenvironment by inhibiting VEGFR. Furthermore, anlotinib promotes the differentiation and maturation of dendritic cells, enhancing their ability to present tumor antigens to T cells. As a consequence, the activation and penetration of the effector T cells in tumor cells are enhanced, which improves the efficacy of toripalimab[17].

Combination anti-PD-1 and targeted therapy is increasingly widely used for treatment of several malignancies such as gastric cancer, non-small cell lung cancer, and liver cancer, but its use is uncommon in ESCC[18-20]. Liu *et al*[5] retrospectively reviewed and analyzed 98 patients with advanced ESCC, wherein 48 patients were administered anlotinib plus an anti-PD-1 and remaining 50 patients received anlotinib monotherapy. Overall, patients receiving the combination therapy showed a longer PFS (5.4 *vs.* 3.0 mo) with a higher ORR (23.9% *vs.* 10.4%) than the patients receiving anlotinib monotherapy[5]. Additionally, Tang *et al*[6] reported that a postoperative recurrent ESCC patient receiving a combination therapy of nivolumab and anlotinib showed CR. Similarly, Jiang and Zhang[4] reported that a patient with chemo-resistant small-cell carcinoma of the esophagus achieved CR after 3 mo of toripalimab plus anlotinib. Our study is the first report where toripalimab in combination with anlotinib is being used as the first-line treatment for advanced or unresectable ESCC. The patient showed CR in 3 mo and has been in remission for up to 14 mo of follow-up with no treatment-related adverse events.

The potential for drug resistance and side effects associated with long-term drug use is a concern, although this did not occur in our case. In addition, since medical insurance can only reimburse a percentage of the cost, the long-term use of such high-priced drugs can further increase the financial burden of patients.

CONCLUSION

Our case report suggests that the combination of toripalimab and anlotinib may be a potential treatment option for advanced or unresectable ESCC. Clinical trials studying the use of this combination for treating ESCC should be conducted in the future to further verify these findings.

FOOTNOTES

Author contributions: Zhong JJ contributed to manuscript writing and editing; Ma DH contributed to data collection; Chen SC contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

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