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CASE REPORT

Primary small cell esophageal carcinoma, chemotherapy sequential immunotherapy: A case report

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Abstract

BACKGROUND

Primary small cell esophageal carcinoma (PSCEC) is aggressive and rare, with a worse prognosis than other subtypes esophageal carcinoma. No definitive and optimum standard guidelines are established for treating it. Herein, we report a case of PSCEC, including a current literature review of PSCEC.

CASE SUMMARY

A 79-year-old male was diagnosed PSCEC with multiple lymph node metastasis thorough computed tomography, positron emission tomography-computed tomography, endoscopy and pathology. Surgery was not suitable for this patient. He was treated with etoposide 100 mg/m^2 and cisplatin 25 mg/m^2 on days 1-3, every 3 wk for 4 cycles. The tumor and lymph nodes became smaller and dysphagia and vomiting symptoms improved. The patient could not tolerate subsequent chemotherapy (CT) because of hematological toxicity; therefore, we performed immunotherapy (durvalumab, 1500 mg) every 4 wk. At present the patient has received 12 cycles immunotherapy over about 1 year. He is still receiving treatment and follow-up.

CONCLUSION

PSCEC with multiple lymph nodes metastasis does not always indicate surgery. CT may extend survival time and improve the quality of life in the absence of surgery. Immunotherapy or immunotherapy plus CT may also work as a treatment for PSCEC.

Key Words: Primary small cell esophageal carcinoma; Diagnosis; Chemotherapy; Immunotherapy; Case report

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Core Tip: A 79-year-old male was diagnosed primary small cell esophageal carcinoma and multiple lymph nodes metastasis thorough computed tomography, positron emission tomography-computed tomography, endoscopy and pathology. Surgery was not suitable for this patient. Instead, he was treated with etoposide and cisplatin chemotherapy regiment, every 3 wk for 4 cycles, which caused the tumor and lymph nodes to shrink. The patient could not tolerate subsequent chemotherapy due to hematological toxicity; therefore, we performed immunotherapy (durvalumab, 1500 mg) every 4 wk. At present, the patient has received 12 cycles immunotherapy over about 1 year and continues treatment and follow-up.

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INTRODUCTION

Primary small cell esophageal carcinoma (PSCEC) is a rare disease, accounting for only 0.8% to 3.1% of all esophageal malignancies[1,2]. The first case was reported in 1952 by McKeown, at present, only about 300 cases of PSCEC have been reported in the world medical literature[3].

PSCEC has an aggressive progression, with early metastasis and high malignancy, and the prognosis is poorer than other subtypes esophageal carcinoma[1]. However, at present, there are no definitive and optimum standard treatment guidelines for PSCEC, though most experts recommend radical esophagectomy, chemotherapy (CT) and radiotherapy (RT) for PSCEC either alone or in combination[4,5]. With the wide application of immunotherapy, perhaps it will become a new treatment[6,7]. Herein we report the case of a 79-year-old man with a PSCEC treated with CT followed by immunotherapy, the tumor has stopped enlarging and has not metastasized, and the patient is no longer experiencing discomfort.

CASE PRESENTATION

Chief complaints

A 79-year-old male was hospitalized for progressive dysphagia, frequent vomiting, and weight lost (approximately 5 kg in 1 mo).

History of present illness

The patient began to experience dysphagia 1 mo prior to examination. Symptoms of obstruction and dysphagia were aggravated, with intermittent chest pain during this month. Food intake decreased, and patient lost 5 kg of weight during this month. Acid reflux and heartburn symptoms were not present, and he did not cough when he swallowed or drank.

History of past illness

The patient is healthy without a history of hypertension or diabetes.

Personal and family history

He was a nonpassive smoker. He did not have a family history of malignancy.

Physical examination

Physical examination does not identify any enlarged lymph nodes in the neck or supraclavicular regions. Cardiopulmonary examination is almost normal without any positive signs.

Laboratory examinations

Blood neuron-specific enolase (NSE) level was 20.80 ng/mL higher than the normal value (16.3 ng/mL), other tumor markers (alpha fetoprotein, CEA, CA-125, CA-199) were all within the normal range.

Imaging examinations

Positron emission tomography-computed tomography and computed tomography demonstrated a tumor in the middle and lower esophagus. Multiple mediastinal lymph nodes were enlarged and were regarded as metastasis (Figure 1A-C). Endoscopy revealed a carcinoma in the esophagus beginning at 28 cm from his teeth and extending to 38 cm, the carcinoma almost blocked 3/4 of esophageal cavity (Figure 1D).

Microscopic examination of hematoxylin-eosin staining tumor slices showed the tumor cells had small oval and spindle cell shape nuclei, ill-defined cell borders, and inconspicuous nucleoli (Figure 2A and B). Immunohistochemistry (IHC) studies showed the tumor Ki-67 index > 80%, Cg-A-positive, p40-positive, Syn-positive (Figure 2C-F).

FINAL DIAGNOSIS

PSCEC, TNM: cT3N2M0, stage III.

TREATMENT

Stage III PSCEC was not suitable for surgery, and the patient did not tolerate concurrent CT plus RT; therefore, he was treated with etoposide 100 mg/m^2 and cisplatin 25 mg/m^2 on days 1-3, every 3 wk. After one cycle, dysphagia decreased and frequent vomiting resolved. It was partial response according to the Recist 1.1 guidelines, and after four cycles of CT, dysphagia completely resolved (Figure 3A). NSE levels in blood also decreased by 6.4 ng/mL. Due to CT toxicities, subsequent therapy was switched to immunotherapy (durvalumab 1500 mg) every 4 wk. According to imaging, the tumor remained stable after 4 cycles of CT and 8 cycles immunotherapy (Figure 3B and C), and NSE blood levels remained normal. Patient did not experience any immune-related adverse events (irAEs) or cancer progressions symptoms for about 1 year. The patient was followed every 3 mo with chest imaging, abdominal ultrasound, brain magnetic resonance and monitored monthly with blood tests.

OUTCOME AND FOLLOW-UP

The patient has received 12 cycles of durvalumab (1500 mg). The tumor and lymph nodes remain stable, and no new metastasis have been identified. the patient has not reported any more dysphagia or frequent vomiting, and continues follow-up and treatment. A timeline showed the whole medical procedure of this case (Figure 4).

DISCUSSION

PSCEC is a rare esophageal malignancy. Because of aggressive biologic behavior and early widespread metastasis, it is generally regarded to have a poor prognosis[8]. The management, treatment, and follow-up strategies are still not sufficiently standardized. Other studies described a median survival of only 8 mo for patients with local disease (LD) and 3 mo for patients with extensive disease (ED)[9].

PSCEC lacks characteristic manifestations in the early stage, which is similar to other types of esophageal carcinoma. Most patients are at an advanced stage at the time of diagnosis, and symptoms include dysphagia, obstruction and/or frequent vomiting, and weight loss.

World Health Organization histological criteria (2004) for small cell lung cancer (SCLC) or SCEC include small, round, oval or spindle-shaped cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or

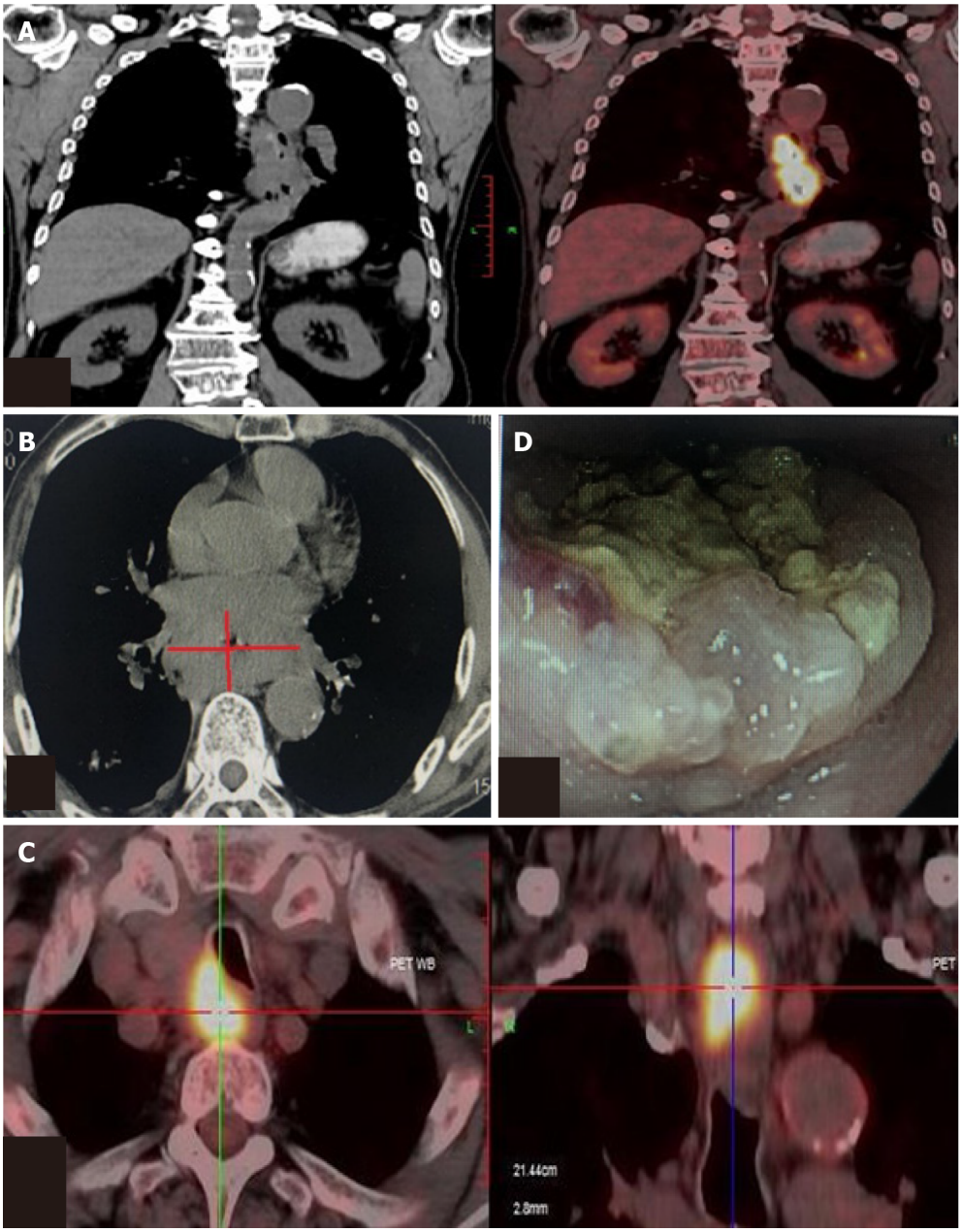

Figure 1 Positron emission tomography-computed tomography, computed tomography and endoscopy demonstrated a tumor sited in the middle and lower esophagus and multiple lymph nodes metastasis. A: Positron emission tomography-computed tomography showed esophageal carcinoma; B: Computed tomography showed esophageal carcinoma; C: Multiple lymph nodes metastasis; D: Endoscopy outcome.

inconspicuous nucleoli. IHC shows positive expression of the tumor markers CK8, AE1/AE3, EMA, Syn, NSE, CD56, Cg-A, and TTF-1[3,10,11]. Wang *et al*[10] showed that high Ki-67 expression was an independent favorable prognostic factor for PSCEC patients[12]. It is generally believed that the Ki-67 index is > 50% in small carcinomas and this tumor Ki-67 index is > 80%. Syn and NSE are expressed in all gastrointestinal small cell carcinomas. This case was Cg-A positive and Syn-positive, and NSE levels were elevated in blood.

PSCEC is like SCLC, with local and distant lymphatic and hematogenous metastasis at first diagnosis, suggesting routine surgery for PSCEC may not be necessary. However, some studies show that esophagectomy can produce the best overall survival for patients with localized or local-advanced cancer, compared to chemoradiotherapy (CRT) or CT alone[13].

Some analysis suggest that surgery could achieve clinical benefits only for patients with LD, combined RT or/and CT might be to extend the survival time patients with regional and extensive[14]. Sun *et al*[15] reported some patients who received surgery and postoperative adjuvant CT achieved a survival of 10 years. PSCEC is a chemical sensitive disease, and CT is one of the most important methods for treating it;

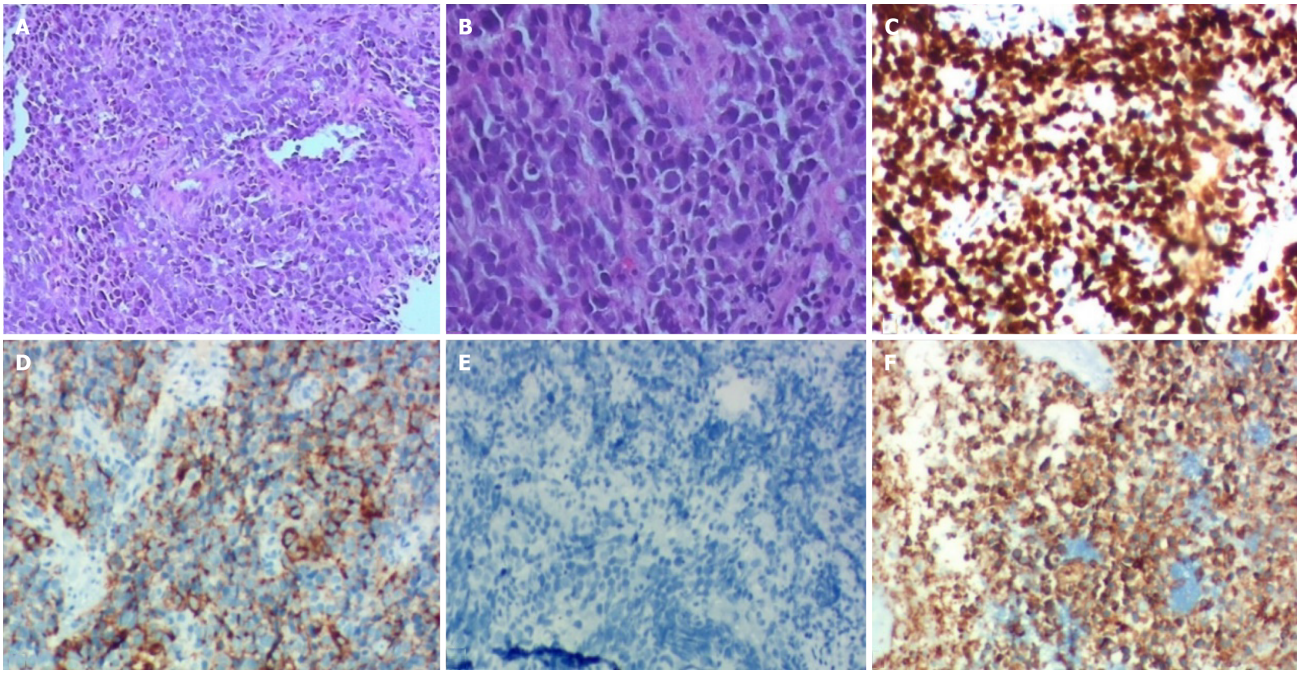

Figure 2 Histopathological and immunohistochemistry examinations. A: The field of vision was completely filled with tumor cells (hematoxylin-eosin staining, × 10); B: Higher magnification showed small oval and spindle cell shape nuclei, ill-defined cell borders, and inconspicuous nucleoli (hematoxylin-eosin staining, × 200); C: Ki-67 (index > 80%); D: Cg-A-positive; E: p40-positive; F: Syn-positive.

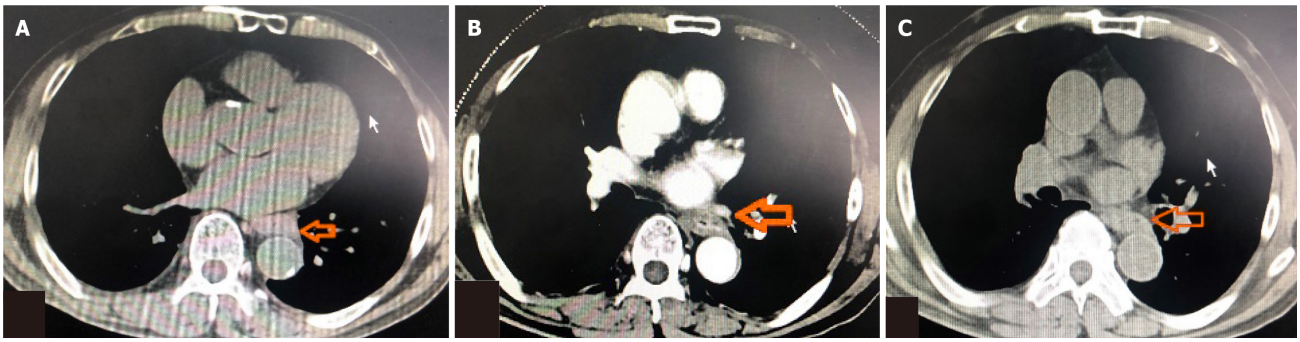

Figure 3 Computed tomography showed the effects of esophageal carcinoma after chemotherapy or immunotherapy. A: After 4 cycles chemotherapy; B: After 4 cycles immunotherapy; C: After 8 cycles immunotherapy.

therefore, it is believed to be the cornerstone of the multimodality therapy, improving the survival time both in LD and ED patients.

Tumor TNM staging has been seen as a significant prognostic factor for survival in patients. Stage I/IIA, the median survival time (MST) for patients who undergo surgery is 29 mo, as compared to 17.4 mo for those who do not receive surgery. Patients with stage II do not prolong the overall survival with radical surgery alone. Patients with stage IIB/III disease who receive CT have a better MST than patients without CT (13.0 mo *vs* 6.1 mo), while those who receive CT combined with RT have a longer MST than patients who receive surgery combined with CT (25.7 mo *vs* 12.3 mo) [16]. CT can greatly improve the survival time of patients with stage III and IV disease [3]. The MST of patients with stage IV disease after CT is three times that of patients who don't receive CT.

Commonly, CT regimens are platinum-based combined with etoposide or irinotecan, while some use docetaxel in combination with platinum[14,17]. In general, PSCEC CT regimens are the same as those used for SCLC. At present, etoposide combined with platinum is first-line CT for PSCEC, and a few studies have showed that docetaxel combined with platinum as a first-line treatment is also effective[18]. Doxorubicin, cyclophosphamide and vincristine should be considered as second-line treatments.

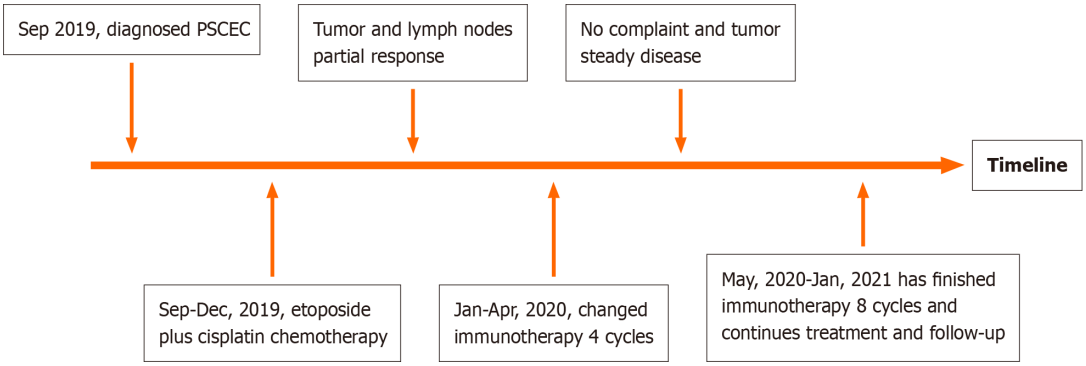

Figure 4 Timeline of the whole medical procedure for this case.

Programmed death-ligand 1 (PD-L1) inhibition (durvalumab 1500 mg) plus EP (etoposide and platinum) has become the new standard for first-line therapy of SCLC; the 12-mo progress-free survival (PFS) was improved with PD-L1 plus EP *vs* EP alone (18% *vs* 5%)[19,20]. Immunotherapy plus CT can improve outcomes in patients with esophageal squamous cell cancer [21]. But no related studies reported immunotherapy or immunotherapy plus CT treated PSCEC. According to histological pathological criteria between SCLC and SCEC, we administered durvalumab (1500 mg every 4 wk) to the patient. Tumor and lymph nodes were unchanged after about 1 year. The patient also did not experience any irAEs, and the PFS reached 12 mo.

PSCEC in the neck or upper segment is treated with RT rather than surgery. Patients are treated with RT to relieve these symptoms quickly. CT and RT alone or combination can bring benefits for ED patients and extend long-term survival time; however, it is not clear if RT alone is useful for stage IV PSCEC.

Several deficiencies in the whole course of treatment remain for our patient. First, CRT was not performed, which might decrease tumor size, and may have a better outcome than CT alone. Second, we did not confirm PD-L1 levels in the tumor or note any tumor pathological changes after immunotherapy. Third, the follow-up time is relatively short and a long-term follow-up is necessary to evaluate the therapeutic efficacy.

CONCLUSION

PSCEC is characterized by early metastasis, advanced stage at diagnosis, and poor prognosis. The prognosis depends on the tumor TNM stage, and the choice of local and/or systemic treatment. PSCEC with stage III or higher are not surgical candidates; however, CT play a role in extending survival time and improving the quality of life. Immunotherapy or immunotherapy plus CT could become another treatment for PSCEC.

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