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## **Cutaneous metastasis from esophageal squamous cell carcinoma: A case report**

Zhang RY *et al.* Cutaneous Metastasis from ESCC

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### **Abstract**

#### **BACKGROUND**

Esophageal cancer is a most common cause of cancer-related death worldwide. Cutaneous metastasis of esophageal squamous cell carcinoma is rare, particularly in diffuse skin metastasis.

#### **CASE SUMMARY**

In this case report, we describe an 82-year-old male who was diagnosed with esophageal squamous cell carcinoma. The tumor was staged as T4N3M1 (Stage IVB). The pathological findings revealed poorly differentiated squamous cell carcinoma of the esophagus. Four months after diagnosis, the patient began chemotherapy, and symptoms were relieved after four cycles of chemotherapy. After that, the patient returned home without a systematic physical examination. One year after diagnosis, the patient realized that the skin of the abdominal wall was hard and rough without pain, and the color became darker than normal skin. Thirteen months after diagnosis, a biopsy of the patient's abdominal lesion revealed that the skin metastasis was derived from the esophagus. And then, the patient received two cycles of apatinib combined

with docetaxel, but the abdominal lesion worsened. So two cycles of nivolumab were administered, but the patient eventually died of multiple organ failure.

## CONCLUSION

This report highlights cutaneous metastasis as a late and untreatable metastasis of esophageal cancer.

**Key Words:** Esophageal carcinoma; Squamous cell carcinoma; Cutaneous metastasis; Immunological checkpoint inhibitor; Chemotherapy; Case report

## INTRODUCTION

Esophageal carcinoma accounts for 3.2% of all new cancer cases worldwide<sup>[1]</sup>. In China, the estimated number of esophageal carcinoma cases in 2015 was 0.37 million<sup>[2]</sup>. Different from European and North American countries, the main pathological type of Chinese patients with esophageal cancer is squamous cell carcinoma, while this is merely 30% in North American countries<sup>[3]</sup>.

Cutaneous metastasis from esophageal carcinoma is rare, and its prevalence is only less than 1%<sup>[4]</sup>. Lookingbill *et al*<sup>[5]</sup> conducted a retrospective study of 4020 cutaneous metastasis patients and found only three primary esophageal squamous cell carcinoma cases. We present a patient with squamous cell carcinoma of the esophagus and metastasis to diffuse cutaneous tissue. This patient only achieved a 4-mo survival time after cutaneous metastasis.

## CASE PRESENTATION

### Chief complaints

An 82-year-old male presented to our clinic and complained of dysphagia and loss of appetite, accompanied by diffuse cutaneous metastasis.

### *History of present illness*

An 82-year-old male presented to our outpatient clinic, and complained of difficulty in dysphagia and loss of appetite, accompanied by acid reflux without nausea and vomiting, from May 2018. The positron emission tomography (PET)/computed tomography (CT) revealed diffuse thickening of the esophagus and stomach wall, with a maximum standard uptake value of 11.2 and bilateral pleural effusion rendering the tumor inoperable (Figure 1A and B). Because the cytology of the patient's pleural fluid revealed pleural metastases, the tumor was staged as T4N3M1 (Stage IVB). The endoscopic study revealed a peripherally protruding neoplasm at 35 cm from the dental arch, which almost completely occluded the esophageal lumen, and a biopsy was taken from the circumferential bulge. The pathological findings revealed poorly differentiated squamous cell carcinoma from the esophagus. Subsequently, chemotherapy was performed: S-1 50 mg d1-14, cisplatin 30 mg d1, 21 d, one period, a total of four cycles (weight, 55 kg; height, 1.62 m; body surface area, 1.64 m<sup>2</sup>). After four cycles of chemotherapy, the patient's symptoms were relieved and the pleural effusion disappeared upon evaluation of the lesion, according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria. Furthermore, after completing the four cycles of chemotherapy, the patient had a partial response (based on the medical records provided by the hospital where the patient previously visited). Afterward, the patient went home. In early March 2019, the patient realized that the skin of the abdominal wall was hard and rough without pain, and the color became darker than the normal skin (Figure 2B). The CT scan of the abdominal showed no obvious changes in skin and subcutaneous soft tissue (Figure 4A). At the same time, we performed a fine needle biopsy of the skin of the changing part (Figure 2B). And pathological results showed that the skin metastasis was derived from the poorly differentiated squamous cell carcinoma of the esophagus (Figure 3). Thus, the patient visited our hospital for a workup for his dysphagia and diffuse cutaneous metastasis. Based on the medical history and pathological findings, the skin metastasis was derived from the poorly differentiated squamous cell carcinoma of the esophagus (Figure 3).

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### *History of past illness*

The patient had a history of diabetes for 20 years and did not regulate the use of drugs. Deny the history of operation.

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### *Personal and family history*

The patient had no history of smoking and occasionally drank alcohol. Furthermore, the patient quit drinking before admission to the hospital.

### *Physical examination*

The patient's vital signs were stable. The physical examination of the abdomen revealed that the skin of the abdominal wall was hard and rough without pain, and the color became darker than normal skin (Figure 2B).

### *Laboratory examinations*

Blood tumor markers: total prostate specific antigen 6.92 ng/mL, serum CA72-4 61.32 U/mL, alpha-fetoprotein 3.65 ng/mL, carcino-embryonic antigen 915.10 ng/mL, serum CA125 90.91 U/mL, CA153 38.24 U/mL, gastrin-releasing peptide precursor 74.40 pg/mL, squamous cell carcinoma antigen 2.20 ug/L, neuron-specific enolase 11.00 ng/mL, serum osteogen CYFRA21-1 5.06 ng/mL.

### *Imaging examinations*

The abdominal CT revealed no obvious changes in the skin and subcutaneous soft tissue (Figure 4A).

## **PATHOLOGICAL EXAMINATION**

Infiltration of cancer cells was observed in the fibrous connective tissue by the puncture. The cancer cells were distributed in nests, with enlarged nuclei, hyperchromatic nuclei, heteromorphism, increased nucleo-plasma ratio, and crowded arrangement (Figure 3A

and B). Further immunohistochemical results showed that skin was positive for CK (Figure 3C), P40 (Figure 3D), P63 (Figure 3E), CK5/6 (Figure 3F), partially positive for P53 (Figure 3G), and about 20% positive for Ki67 (Figure 3H). The pathological results revealed that the skin metastasis was derived from the poorly differentiated squamous cell carcinoma of the esophagus (Figure 3).

### **FINAL DIAGNOSIS**

The final diagnosis of the presented case was esophageal squamous cell carcinoma, and relapse with cutaneous metastasis after first-line chemotherapy treatment.

### **TREATMENT**

The patient received systemic treatments, including second-line chemotherapy with apatinib and docetaxel.

### **OUTCOME AND FOLLOW-UP**

After two cycles of chemotherapy, the patient's abdominal wall cutaneous metastasis lesions significantly increased. Subsequently, nivolumab (120 mg, intravenous infusion on day one) treatment was immediately applied. Unfortunately, after two cycles of nivolumab treatment, the patient's condition did not alleviate, and the skin lesions increased. Eventually, the patient died of multiple organ failure.

### **DISCUSSION**

<sup>2</sup> In contrast to adenocarcinoma, squamous cell carcinoma is more likely to localize near the tracheal bifurcation, has a proclivity for earlier lymphatic spread, and is associated with a poorer prognosis<sup>[6]</sup>. In Eastern Europe and Asia, squamous cell carcinoma is the most common histology, while adenocarcinoma is the most widespread in North America and West Europe<sup>[7]</sup>.

The meta-analysis conducted by Strickley *et al*<sup>[8]</sup> indicated that the overall incidence of cutaneous metastasis is 5.3%. Melanoma and breast cancer is the most prone to



metastasize to the skin and subcutaneous tissue<sup>[5,7]</sup>. However, other malignancies such as lung, colon, head, and neck, and hematologic diseases also have been described with a degree of frequency<sup>[8]</sup>. Furthermore, esophageal carcinoma cutaneous metastasis is rare, especially in esophageal squamous cell carcinoma, and the risk of skin metastasis is lower. However, esophageal adenocarcinoma more commonly metastasizes to the skin<sup>[4]</sup>. The manifestation of skin metastasis from esophageal cancer reported by most of the literature is scattered nodules that are rarely painful<sup>[9]</sup>. The retrospective analysis reported by Ferreira *et al*<sup>[10]</sup> revealed that similar to esophageal cancer, adenocarcinoma is the histological type of lung cancer most prone to skin metastasis. However, the most common clinical manifestation of skin metastasis of lung cancer is single nodules, and the most common site is the head<sup>[11]</sup>. Different from esophageal and lung cancer, typical ductal or lobular carcinoma tends to involve skin metastases to the thorax and abdomen, occasionally with hardened, erythematous plaques<sup>[12]</sup>. Nevertheless, the most common clinical presentation is single or multiple skin-stoned or pink nodules<sup>[13]</sup>.

Different from the literature, the present patient's skin was mainly characterized by diffuse thickening and roughness. Cutaneous metastasis from esophageal carcinoma is rare and predominantly occurs in late tumor status. This suggested a rapid disease, as shown in Figure 4: (A) the chest CT presented pleural effusion, suggesting that the disease recurred again; (B) the results suggested ascites effusion, lower esophagus dilation, and esophageal wall thickening; and (C) after two cycles of nivolumab treatment, the effusion increased, and the lower esophagus thickening became obvious; the abdominal CT revealed that the abdominal wall skin was thicker than the other parts, but no subcutaneous nodules were observed. Imaging diagnosis can easily overlook the skin thickening progression and impending generalized metastatic spread<sup>[14]</sup>. Patients with esophageal cancer cutaneous metastasis have a poor prognosis. The average survival time after the development of cutaneous metastases is approximately only four months<sup>[5]</sup>.

Fine-needle aspiration cytology is a rapid and safe technique that can be used for the diagnosis of skin metastases. The <sup>4</sup>critical evaluation of cytomorphological features,

along with relevant clinical details, can help in the localization of unknown primary sites in some cases. Furthermore, the critical assessment of the morphological features of cells and the associated clinical details can help determine the source of the skin metastatic lesion<sup>[15]</sup>.

Chemotherapy is the standard treatment for advanced esophageal cancer with distant metastases. Commonly used agents include 5-fluorouracil, platinum agents, and taxanes. However, the objective response rate of platinum-containing dual-agent chemotherapy for esophageal squamous cell carcinoma is not high<sup>[16-18]</sup>. Immunotherapy with antibodies against PD-1 immunological checkpoints has exhibited optimistic results in the treatment of esophageal squamous cell carcinoma patients. A phase 2 clinical study confirmed the nivolumab monotherapy for advanced esophageal squamous cell carcinoma, which includes 64 patients. The primary endpoint was the objective response rate, and the objective response rate was 17%. The conclusion suggests that nivolumab showed promising activity with a manageable safety profile in patients with esophageal advanced squamous-cell carcinoma refractory or intolerant to standard therapies<sup>[19]</sup>. Therefore, investigators attempted to apply nivolumab for the treatment of esophageal cancer with skin metastases. In the present case, the patient was older (82 years old), received third-line treatment, had a physical status score of 2 points, and had multiple metastases with a heavier tumor burden. Hence, the treatment response at the immune checkpoint was poor<sup>[20]</sup>. Furthermore, the immune checkpoint inhibitor took a long time to achieve significant anti-tumor effects. After two cycles of immunological checkpoint inhibitor treatment, the tumor progressed, and the patient died. Therefore, based on the clinical trial data, it is recommended to apply the immune checkpoint inhibitor early. In summary, extensive cutaneous metastasis of esophageal squamous cell carcinoma is extremely rare, and distributed skin metastases indicate that the tumor has advanced, and the prognosis is poor. The best treatment is timely systemic chemotherapy. For elderly patients with extensive skin metastases, immunotherapy after second-line or more than third-line treatment is less effective. This may be correlated to the low immunity of the patient, the lack of immune cell



reserves, and the inability to mobilize effective immune cells to clear the tumor. But that's just speculation, and more experiments are needed.

## **CONCLUSION**

Diffuse cutaneous metastasis of esophageal squamous cell carcinoma is rare, and second-line chemotherapy and immunological checkpoint inhibitor treatment are not effective.

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## Figure Legends

**Figure 1 The positron emission tomography (PET)/computed tomography image.** A, B: Diffuse thickening of the esophagus with an elevated standard uptake value, and bilateral pleural effusion.

**Figure 2 The cutaneous metastasis disease progress.** A: In July 2018 the normal abdominal wall skin at the beginning of diagnosed esophageal squamous cell carcinoma; B: In March 2019, the patient realized that the skin of the abdominal wall was hard and rough, and the color became darker than normal skin. At the same time, a fine needle biopsy of the skin of the changing part was performed; C: In early May 2019, the patient's cutaneous metastasis significantly increased before the anterior chest wall; D: In early June 2019, the color of the skin lesions was lighter than before. The texture was soft, and the skin lesion did not expand; E, F: At the end of June, the patient's cutaneous metastasis transferred to the anterior chest wall and abdominal wall, as well as to the neck and lower limbs.

**Figure 3 Histological patterns of skin lesions.** A, B: The hematoxylin and eosin staining of sites for the fine needle biopsy specimen revealed esophageal squamous cell carcinoma in A (magnification  $\times 10$ ), B (magnification  $\times 20$ ); C: Representative immunohistochemical staining for CK in the skin (magnification  $\times 20$ ); D: Representative immunohistochemical staining for P40 in the skin (magnification  $\times 20$ ); E: Representative immunohistochemical staining for P63 in the skin (magnification  $\times 20$ ); F: Representative immunohistochemical staining for CK5/6 in the skin (magnification  $\times 20$ ); G: Representative immunohistochemical staining for P53 in the

skin (magnification  $\times 20$ ); H: Representative immunohistochemical staining for Ki67 in the skin (magnification  $\times 10$ ).

**Figure 4 The abdominal computed tomography of the skin and subcutaneous soft tissue.** A: The chest computed tomography (CT) presented pleural effusion, suggesting that the disease recurred again; B: This suggested ascites effusion, as well as lower esophagus dilation and esophageal wall thickening; C: After two cycles of nivolumab treatment, the effusion increased, and the lower esophagus thickening became obvious. The abdominal CT shows that the abdominal wall skin was thicker than the other parts, but no subcutaneous nodules could be observed. Imaging diagnosis can easily overlook skin thickening.

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