

Primary malignant melanoma of the esophagus treated by endoscopic submucosal dissection: A case report

MEI WANG¹, JIANPING CHEN¹, KEWEN SUN¹, YUN ZHUANG¹, FU XU¹,
BIN XU², HONGYU ZHANG³, QING LI⁴ and DACHUAN ZHANG⁴

Departments of ¹Digestion, ²Tumor Biological Treatment, ³Oncology and ⁴Pathology,
The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu 213003, P.R. China

Received February 8, 2015; Accepted May 18, 2016

DOI: 10.3892/etm.2016.3482

Abstract. Primary malignant melanoma of the esophagus (PMME) is a rare malignant neoplasm of the esophagus. In the majority of cases, the disease originates in the mucosal layer of the esophagus, which is similar to other types of esophageal cancer. With the development of endoscopic submucosal dissection (ESD), endoscopic resection is possible for cases in which melanomas are limited to the mucosal and submucosal layer. However, few studies report the efficiency of ESD for PMME, and no studies perform long-term follow-up. The present study reported the case of a 71-year-old PMME patient who was successfully treated by ESD at The Third Affiliated Hospital of Soochow University (Changzhou, China) in October 2011, with a follow-up of >3 years conducted.

Introduction

Primary malignant melanoma of the esophagus (PMME) has only ~300 cases reported in the literature (1,2). It is a rare malignant disease, accounting for 0.1-0.2% of esophageal malignancies. Definitive diagnoses depends on pathology and immunohistochemical examination with positive results for S-100, human melanoma black (HMB)-45 and melanoma-specific antigen (Melan-A) proteins. PMME has a 5-year survival rate of 2.2-4.2% and the present standard treatment is surgical resection (3). In recent years, few cases of PMME patients undergoing endoscopic mucosal resection (EMR) have been reported. At present, endoscopic submucosal dissection (ESD) is used to treat tumors originating from the mucosal or submucosal layer due to the possibility of en bloc resection of

lesions regardless of their size and shape (4). Theoretically, due to the similarity of the site of origin of PMME compared with other operable tumors, ESD may be a viable option for its treatment. However, to the best of our knowledge, no case of PMME treated with ESD has been reported, and the follow-up requirements and complications of PMME subsequent to endoscopic treatment remain unexplored.

The present study reports the case of a 71-year-old PMME patient who was treated by ESD at the Third Affiliated Hospital of Soochow University (Changzhou, China) in 2011. In addition, a follow-up period of >3 years was conducted.

Case report

A 71-year-old female patient was admitted to the Third Affiliated Hospital of Soochow University with complaints of progressive dysphagia in December 2011. The patient had been diagnosed with breast carcinoma and had undergone radical surgery >2 years earlier. Physical examination was normal and revealed no skin lesions. Esophagogastrosocopy indicated an irregularly shaped pigmented polypoid mass located between 29 and 32 cm from the incisors (Fig. 1A). Biopsy was performed and the mass was found to be a primary malignant melanoma. In addition, endoscopic ultrasound (EUS) was performed and indicated a hyperechoic mass originating from the mucosal layer, which was 0.8x2.8 cm in size with a pedicle diameter of ~0.8 cm (Fig. 1B). The mass originated from the mucosal layer and displayed a tubiform structure in the center with no echo, while the submucosal layer and muscularis propria were intact. Chest and abdominal computerized tomography (CT) indicated no metastasis to the lymph nodes, mediastinum or the lungs. Further examinations also ruled out distant metastasis. Additionally, the patient declined surgery for the PMME, and was thus treated with ESD (Fig. 2), subsequent to providing informed consent.

Prior to the procedure, the patient received conscious sedation [using midazolam (Jiuxu Pharmaceutical Co., Ltd., Zhejiang, China) or propofol (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany)] in the left lateral position. Following the submucosal injection, the overlying mucosa was dissected circumferentially. Then, the mass was resected. The primary techniques included the use of a standard therapeutic endoscope (GIF-Q260; Olympus Corporation, Tokyo, Japan),

Correspondence to: Dr Mei Wang or Dr Jianping Chen, Department of Digestion, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou, Jiangsu 213003, P.R. China

E-mail: 517158436@qq.com

E-mail: chenjianping2016@outlook.com

Key words: primary malignant melanoma of the esophagus, treatment, endoscopic submucosal dissection

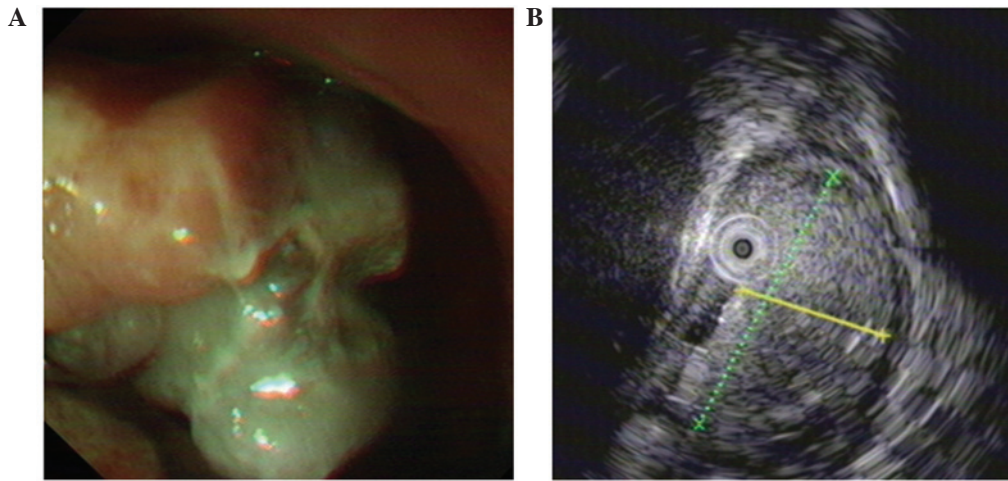


Figure 1. Endoscopic examination. (A) A black-pigmented, irregular elevated mass was located 29-32 cm from the incisors. (B) Endoscopic ultrasound revealed that the mass originated from the mucosal layer.

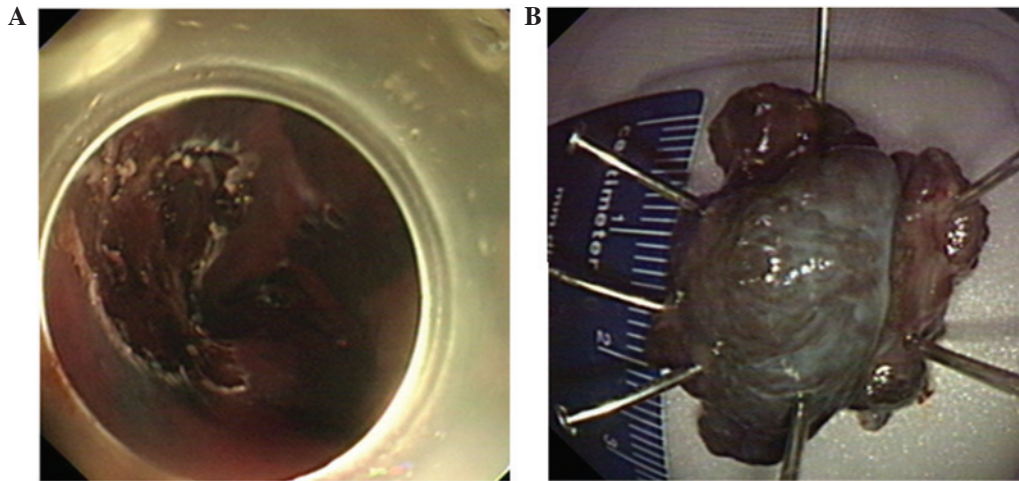


Figure 2. (A) Large artificial ulcer created following endoscopic submucosal dissection. (B) Specimen resected from the patient (size, 2.5x2.8 cm).

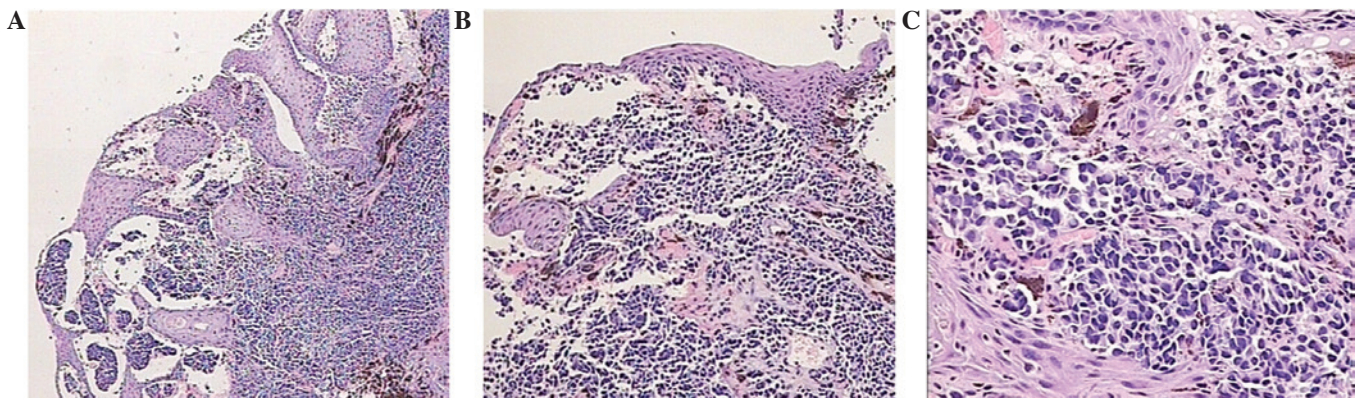


Figure 3. Histological examination of the resected esophageal mass. A subepithelial pigmented cellular tumor is displayed, stained with hematoxylin and eosin and observed at magnifications of (A) x40, (B) x100 and (C) x200.

insulated-tip knife (KD-640L; Olympus Corporation) and a hook-knife (KD-620UR; Olympus Corporation). Subsequent to fasting for 3 days after surgery, the patient was allowed to eat. The post-operative white blood cell count was normal and the patient did not complain of discomfort. Pigmented cellular tumor

was stained with hematoxylin and eosin, and positive HMB-45 (A-AH10203; Abgent, San Diego, CA, USA) in immunohistochemical examination confirmed the diagnosis of a PMME (Fig. 3). Following ESD, the patient received three cycles of immunotherapy. Ipilimumab was used as the immunotherapy

for 3 cycles, which is a monoclonal antibody that blocks the checkpoint of cytotoxic T-lymphocyte-associated protein 4 (180 mg per 3 weeks). Follow-up esophagogastrosopy examinations and CT scans showed no signs of disease recurrence for >3 years. The latest clinical follow-up was in January 2016, and the esophagogastrosopy examinations and CT scans showed no signs of disease recurrence. The patient has had a normal life for >4.5 years.

Discussion

PMME is an aggressive and fatal disease associated with poor prognosis, and the incidence of PMME accounts for 0.1-0.2% of esophageal malignancies (5). It typically occurs within the lower two-thirds of the esophagus due to the presence of a high concentration of melanin pigment. The etiology and natural course of the disease remains unknown; however, several studies have hypothesized that esophageal melanocytosis may be a precursor to PMME (6,7). This melanoma tends to metastasize readily via the hematogenous and lymphogenous routes. The most common sites of metastases are the liver, mediastinum, mediastinal lymph nodes, the lungs and the brain (8). The symptoms of PMME are not unique compared with other types of esophageal malignancies. The most common complaint include dysphagia and retrosternal pain. HMB-45, AE1/AE3 and S-100 cytoplasmic proteins are the monoclonal antibodies most frequently used to identify PMME (2,3).

Recently, EUS has been employed to identify the depth of invasion and the node status in patients diagnosed with PMME (9). On EUS, PMME appears as a hypoechoic mass or with mixed echogenicity compared with the surrounding healthy tissue (9). It has previously been reported that endoscopic ultrasound guided fine-needle aspiration may be used to diagnose PMME (10). The proposed criteria for the diagnosis of PMME are the following: i) The mass possesses the characteristic structure of a melanoma, containing melanin; ii) the adjacent epithelium contains melanocytes; iii) the mass arises from the area of junctional changes in the squamous epithelium; and iv) metastasis of malignant melanoma from other parts of the body is excluded (11).

There is currently no gold standard for the treatment of PMME. Furthermore, it has been reported that 30-40% of patients with PMME present nodal or distant metastases at diagnosis, and ~85% will succumb as a result of distant metastasis regardless of the treatment (2). It is agreed that treatment should be adjusted individually according to the tumor size, location, presence of metastases, patient age and comorbidities observed. However, surgical resection should be considered as the first line treatment for all patients with PMME, since radical surgical extirpation increases the chances of long-term survival (12).

For patients that decline or are unable to undergo radical surgery, palliative treatment is an alternative method and includes radiotherapy, chemotherapy and immunotherapy. However, the aforementioned therapies are not successful in the treatment of PMME, and the mean survival time has been reported to be 13.4 months (10). In recent years, novel therapeutic agents have been approved for the treatment of melanoma; however, few randomized clinical trial studies have supported their efficacy (13). Thus, the resection of the tumor remains the only viable treatment with the potential to cure patients with PMME.

In the present study, the patient had a history of breast carcinoma and had previously undergone surgery 2 years prior to presenting with dysphagia. Subsequent to excluding breast metastasis, the tumor was diagnosed as PMME. As the patient declined radical surgery, ESD was performed, followed by three cycles of immunotherapy. Follow-up examinations with endoscopy and CT revealed that ESD had successfully removed the tumor the entire tumor.

To the best of our knowledge, only a limited number of reports have described the use of endoscopic treatment for PMME (14-16). Kastl *et al* previously described the implantation of a metal stent to alleviate PMME symptoms, which improved the quality of life in the patient (17). Local endoscopic laser ablation may also serve a role in the palliation of locally advanced tumors that are unresectable (18,19). Furthermore, Miyatani *et al* reported a case involving a slow growing flat-type PMME that was successfully treated by cap-assisted EMR, with no evidence of recurrence during the 20-month follow-up (15). Compared with EMR, the ESD technique enables the en bloc resection of lesions regardless of their size and shape. In 2013, Eleftheriadis *et al* reported a unique case of PMME undergoing successful treatment with ESD and described an uneventful 8-month follow-up period (20).

In the case presented in the current study, the neoplasm originated from the mucosal layer. The patient refused radical surgery, and thus ESD was performed given the large size of the mass. The treatment successfully removed the PMME mass. Notably, this is the first study to describe a case of PMME undergoing treatment with ESD followed by a long-term follow-up period.

In conclusion, to the best of our knowledge, this study is the first to describe the long-term efficacy of ESD for the treatment of PMME. The result of the present study revealed that ESD may be an alternative option to EMR for the treatment PMME in patients that do not present distant metastasis.

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