Primary malignant melanoma of the esophagus: A case report and review of the literature

WEN JIANG, ZHENGYUN ZOU and BAORUI LIU

The Comprehensive Cancer Centre, Drum Tower Hospital, Medical School and Clinical Cancer Institute of Nanjing University, Nanjing, Jiangsu 21000, P.R. China

Received March 25, 2014; Accepted October 29, 2014

DOI: 10.3892/ol.2015.3014

Abstract. Primary malignant melanoma of the esophagus (PMME) is a rare malignancy and the prognosis is typically poor. There is currently a lack of appropriate treatment strategies and clear guidance. The current study presents the case of a 65-year-old female with a two-month history of progressive dysphagia, the investigations of which resulted in a diagnosis of PMME. The patient was treated with a radical transhiatal esophagectomy with subcarinal lymphadenectomy followed by combined chemoimmunotherapy. The patient remains alive with no evidence of tumor progression at the 12-month follow-up. The purpose of the present study was to report a new case and to review the recent relevant literature regarding the treatment of PMME.

Introduction

Malignant melanoma exhibits a clear demographic and ethnic disparity, being more common in Caucasians. Malignant melanoma has the highest incidence in Queensland, Australia (1), and is the fifth most commonly diagnosed cancer in the United States (2). Compared with the high incidence of malignant melanoma found in this population, the incidence in non-Caucasians is low, therefore, the majority of research on melanoma has focused on Caucasian populations. However, primary gastrointestinal melanoma is relatively rare in the Asian population and the literature surrounding this is limited. Primary malignant melanoma of the esophagus (PMME) is a rare malignant disease, accounting for only 0.1-0.2% of all esophageal neoplasms. The mean survival time from diagnosis is only 13.4 months, and the five-year survival rate is 4.2% worldwide (3,4).Definitive diagnoses may be confirmed by pathological analysis and positivity for S-100, human melanoma black (HMB)-45 and melanoma-specific antigen (Melan-A) proteins on immunohistochemical examination. Surgical extirpation is the standard treatment for PMME. The current study presents a case of PMME in a Chinese female. Written informed consent was obtained from the patient's family.

Correspondence to: Professor Baorui Liu, The Comprehensive Cancer Centre, Drum Tower Hospital, Medical School and Clinical Cancer Institute of Nanjing University, 321 Zhongshan Road, Nanjing, Jiangsu 21000, P.R. China
E-mail: baoruiliu@nju.edu.cn

Key words: primary malignant melanoma of the esophagus, esophagus, malignant melanoma

Case report

In February 2013, a 65 year-old female was admitted to the Drum Tower Hospital (Nanjing, China) with a two-month history of dysphagia. An upper gastrointestinal barium esophagogram was conducted and revealed an intraluminal peduncular mass extending into the esophagus (Fig. 1A). Endoscopic examinations showed a 2.0x4.0-cm neoplasm with black pigmentation; the neoplasm protruded into the esophageal lumen and was located 30-33 cm from the incisors, with three flat, black-pigmented, 0.5x1.0-cm mucosal lesions (Fig. 2). Biopsy specimens identified foci cells containing melanin (Fig. 3). No primary cutaneous or ocular lesions were detected. Subsequent to excluding other primary sites by computed tomography (CT; Fig. 1B), a PMME was suspected.

As a result, an esophagectomy with extensive lymph node dissection was performed on February 19, 2013. Histologically, the invasion of the tumors was limited to the submucosal layer and no lymph node metastasis was detected. Evaluation of the resected specimen demonstrated malignant melanoma *in situ*, and subsequent immunohistology revealed that the tumor cells were positive for the Melan-A, HMB-45, and the S-100 protein (Fig. 4), resulting in a diagnosis of melanoma.

Next, two cycles of combined dendritic cell (DC)-based immunotherapy were administered. The first cycle consisted of adjuvant intravenous fotemustine (100 mg/m^2, day 1) and intravenous oxaliplatin (100 mg/m^2, day 1) chemotherapy, however, due to the severe gastrointestinal reaction experienced by the patient, chemotherapy was terminated. Instead, the patient was treated with traditional Chinese medicine (20 mg ginsenoside Rg3, twice daily).

To date, the results of the most recent physical examinations and blood tests, i.e., an esophagogastroduodenoscopy conducted in April 2013 and a CT scan performed in August 2013 (Fig. 1C), have been unremarkable. The patient was in a good general condition for 12 months post-surgery.

An endoscopic evaluation in May 2012 revealed a few granule-like spots scattered in the lower esophagus, with no melanin pigment (Fig. 5), indicating squamous epithelial hyperplasia. The patient exhibited no clinical symptoms therefore no further treatment was administered.

Discussion

PMME is characterized by aggressive behavior and a poor prognosis, even following surgical resection. The average age of onset is 60.5 years, which is younger than that of esophageal carcinoma patients. The incidence of PMME in males is higher than in females, with a ratio of 2:1 (3,4). The majority of PMME patients present with the complaints of dysphagia, non-specific retrosternal pain and weight loss. Occasionally, hematemesis and melena are observed. The most common form of recurrence for PMME is distant hematogenous metastasis, as opposed to lymph node or regional recurrence. In the majority of patients exhibiting tumors later than stage Ib, this recurrence has been found to occur within ~1 year of surgery (5). In addition, ~90% of PMME lesions are located in the distal two-thirds of the esophagus (6). Mehra *et al* (7) confirmed the role of tumor thickness as a prognostic marker of mucosal melanoma; the survival time of patients with mucosal melanoma depends on the primary's T-stage at the time of diagnosis. While, no similar studies particularly regarding PMME were found in the literature.

Even though the first case of malignant melanoma of the esophagus was reported by Baur (8) in 1906, the condition was considered to metastatic, originating from other sites of malignant melanoma. This did not change until 1963 when De La Pava (9) reported the presence of typical melanocytes in the esophageal epithelium. Volpin *et al* (10) identified that 238 cases of PMME had been reported up to early 2001 and that, by 2011, 337 cases had been reported (11). A study by Ohashi *et al* (12) revealed that the rate of esophageal melanocytosis was 7.7% among healthy populations at autopsy and 29.9% among surgical esophageal carcinoma cases in Japanese patients. Furthermore, the results indicated that the increase in melanocytes observed in areas of hyperplastic epithelium and chronic esophagitis may act as precursor lesions for malignant melanoma in the esophagus.

The PMME diagnostic criteria defined in the study by Allen and Spitz (13) include: i) A typical histological pattern of melanoma and the presence of melanin granules within the tumor cells; ii) an origin in an area of junctional change within the squamous epithelium; and iii) junctional activity with melanotic cells in the adjacent epithelium. These criteria, the presence of *in situ* melanoma and/or satellite tumors with no previous history of cutaneous melanoma, and a systematic investigation with pathological examination are required for a definitive diagnosis of PMME.

According to endoscopy, PMME is characterized by a well-circumscribed, elevated and pigmented tumor, partially covered by healthy mucosa, and rarely accompanied by ulcers. Although the unique black pigmentation is an established characteristic of PMME, 10-25% of melanomas may exhibit a variety of other colors, including tan, dark brown, black, blue, red and occasionally light gray. Conversely, melanomas that lack pigment also exist; these are termed amelanotic melanomas (14,15). Bisceglia *et al* (11) presented a case of primary malignant melanoma of the esophagus of the amelanotic variant in a 69-year-old male, however, cases of amelanotic melanomas are not common; Terada (16) reviewed 910 consecutive esophageal biopsies obtained

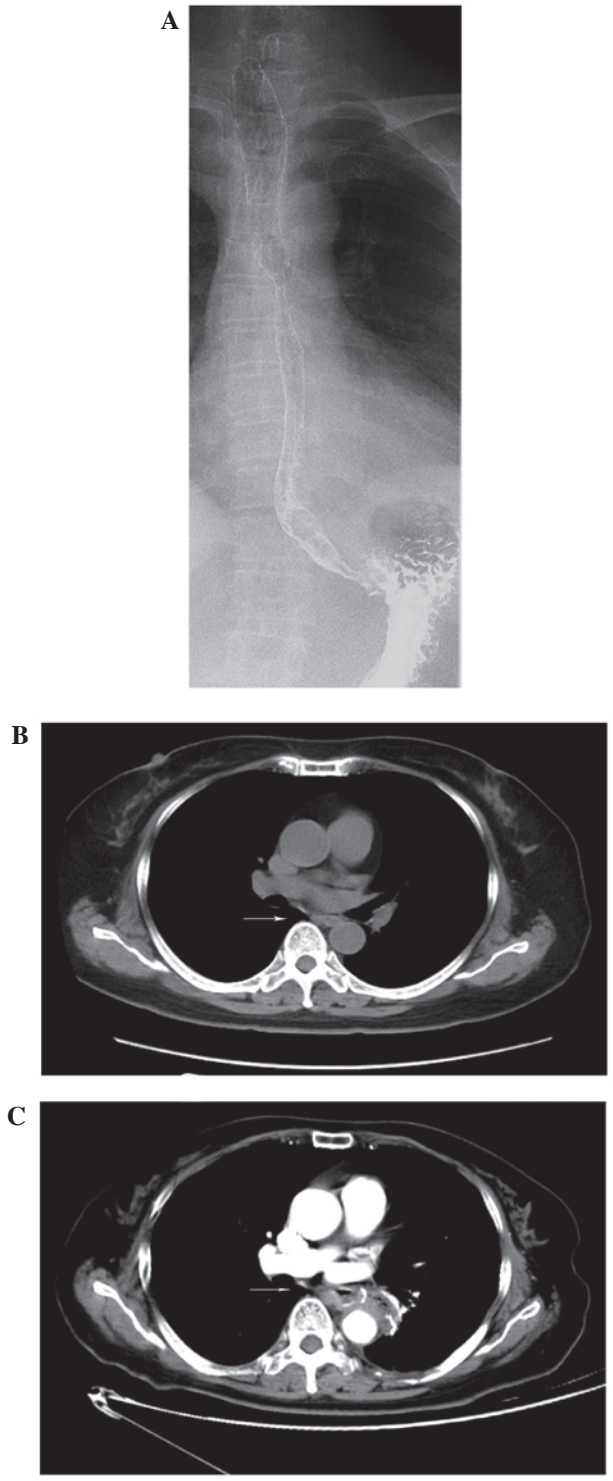

Figure 1. (A) Upper gastrointestinal barium esophagogram findings showing a circular defect in the lower esophagus from February 8, 2013. (B) Pre-surgical computed tomography (CT) scan showing the thickness of the middle esophagus wall, conducted on February 16, 2013. (C) Post-surgical CT scan demonstrating no thickness of the middle esophagus wall, conducted on August 14, 2013.

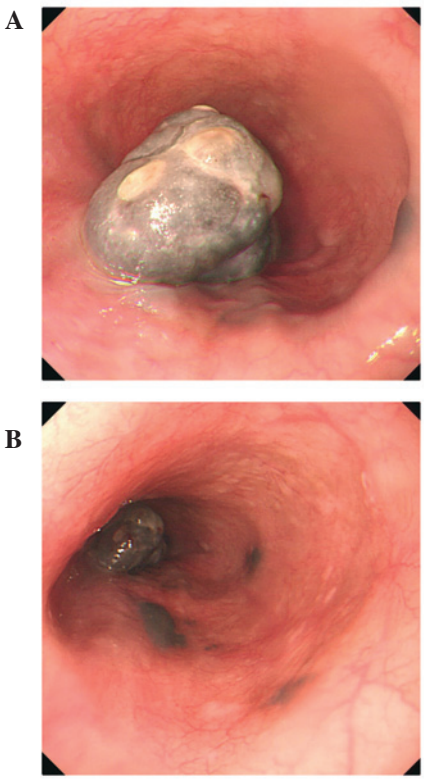

Figure 2. (A) Polypoid tumor measuring 2.0x4.0 cm, with black pigmentation. (B) Three flat, black-pigmented mucosal lesions (0.5x1.0 cm).

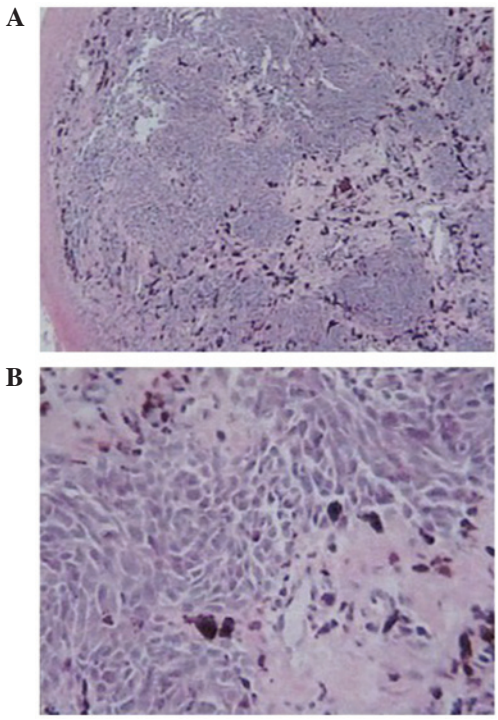

Figure 3. Histochemical evaluation of the biopsy specimens revealing a malignant melanoma. The tumor contained variously pigmented bizarre cells. (A) Hematoxylin and eosin stain; magnification, x40. (B) Hematoxylin and eosin stain; magnification, x200.

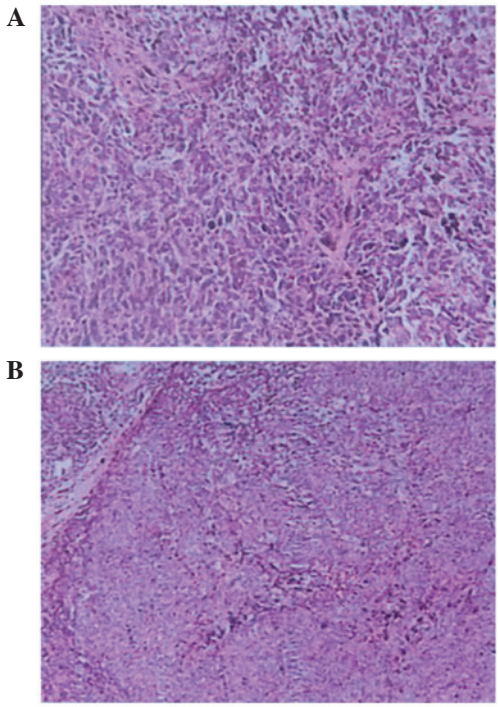

Figure 4. Melanocytic cells exhibiting abundant melanin pigment. The tumor contained variously pigmented bizarre cells. (A) Hematoxylin and eosin stain; magnification, x100. (B) Hematoxylin and eosin stain; magnification, x40.

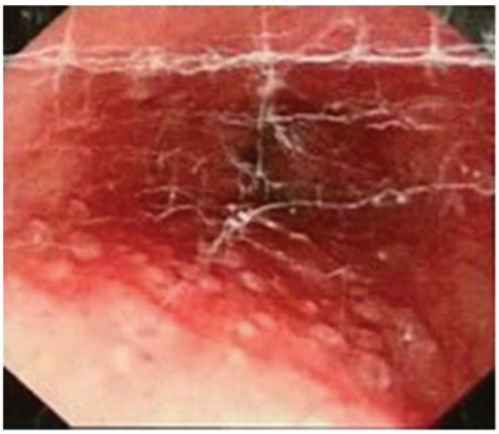

Figure 5. Numerous granule-like spots scattered in the lower esophagus with no melanin pigment.

by the Department of Pathology, Shizuoka City Shimizu Hospital (Shimizu, China), in the previous 15 years, and identified only two cases of primary amelanotic malignant melanoma (0.2%).

Biopsies may provide definitive diagnoses, however, a number of patients have been previously misdiagnosed due to the absence of melanin granules. Thus, immunohistochemical investigations are required for a definitive diagnosis; this includes positive immunohistochemical staining for S100 protein, HMB-45 and Melan-A (15).

No gold standard has been established for the treatment of PMME. Kimura *et al* (17) reported the use of endoscopic mucosal resection for the treatment of early PMME, and recorded no recurrence after 18 months. Consistent with this finding, Cheung *et al* (18) evaluated the Surveillance, Epidemiology and End Results database of primary

gastrointestinal melanomas (1973-2004) and identified complete surgical resection as the only identifiable treatment strategy that significantly improved survival in PMME patients. Therefore, the present study proposes that the timely surgery received by the current patient was significantly associated with the outcome, as the patient remained in good condition 12 months after esophagectomy.

Alternative non-surgical or surgical-adjuvant therapies for PMME patients include chemotherapy, chemoradiotherapy, endocrine therapy and immunotherapy, however, these treatment strategies have yet to be fully evaluated. Nevertheless, even in those patients who were successfully administered these treatments, the majority also underwent surgery (19-23).

Uetsuka *et al* (20) reported a long-term eight-year survival period in an advanced PMME patient who underwent a radical esophagectomy and lymphadenectomy, pre-operative and post-operative chemoendocrine therapy, and immunohormone therapy. The treatment course consisted of 200 mg/day dacarbazine for five days, 100 mg nimustine for one day, 35 mg/day cisplatin for three days and 20 mg/day oral tamoxifen for seven days.

As extremely efficient antigen-presenting cells, DCs are essential for the initiation of the T-lymphocyte-dependent specific immune response. The study by Asakage *et al* (21) was the first to report a case of PMME treated with adjuvant dendritic cell therapy following esophagectomy, which exhibited no recurrence 30 months after surgery. Additionally, Ueda *et al* (20) was the first to report on the effect of active specific immunotherapy using monocyte-derived DCs pulsed with the epitope peptides of melanoma-associated antigens (MAGE)-1 and -3. This novel technique was administered to two HLA-A24-positive PMME patients. Prior to specific immunotherapy, the patients each underwent a radical esophagectomy with regional lymphadenectomy, followed by treatment with dacarbazine, nimustine, vincristine and interferon-α as adjuvant chemotherapy. One of the patients was treated with active specific immunotherapy focusing on a large abdominal lymph node metastasis. The patient survived for 12 months subsequent to the initiation of immunotherapy, with a stable disease state for the first five months. In the second patient, immunotherapy was administered post-operatively following adjuvant chemotherapy. No tumor recurrence was observed for 16 months after the immunotherapy and the patient remains alive 49 months after esophagectomy (22).

Successful therapeutic cases of PMME using completely non-surgical treatment strategies have been reported, albeit only sporadically. For example, in one previous study, two patients who were considered unsuitable for surgery due to their age and general poor health were treated with a combination of external radiotherapy and hyperthermia (HT) (23). A total dose of 35 Gy external radiotherapy was administered as seven fractions of 5 Gy twice a week, and combined with external and intraluminal HT once a week (optimal temperature, 43˚C). The results varied, with one patient succumbing to a fast-growing distant metastasis 11 months post-treatment, and the other patient achieving complete remission. This second patient remained alive and in good general condition at 15 months post-treatment, with no signs of local recurrence or distant metastasis.

The present study reports a rare case of PMME in a female patient. Treatment recommendations for PMME patients are based almost exclusively upon small, retrospective studies; systemically established optimal management strategies remain unknown and require investigation. Surgical resection is currently the preferred treatment strategy for PMME, however, the prognosis of affected patients remains extremely poor, with a reported median overall survival period of 10-14 months (3,4). The majority of patients succumb due to fast disease recurrence even after curative resection. In conclusion, considering the typically poor outcomes of PMME patients, it is possible that the treatment strategy received by the current patient (chemotherapy, immunotherapy, esophagectomy and traditional Chinese medicine treatment), particularly esophagectomy, may have contributed to the patient's good condition 12 months after surgery.

References

1. Curado MP, Edwards B, Shin HR, *et al*: Cancer Incidence in Five Continents. No. 160, Volume IX, IARC Scientific Publications, Lyon, 2007.
2. Jemal A, Siegel R, Ward E, *et al*: Cancer statistics, 2009. CA Cancer J Clin 59: 225-249, 2009.
3. Sabanathan S, Eng J and Pradhan GN: Primary malignant melanoma of the esophagus. Am J Gastroenterol 84: 1475-1481, 1989.
4. Chalkiadakis G, Wihlm JM, Morand G, *et al*: Primary malignant melanoma of the esophagus. Ann Thorac Surg 39: 472-475, 1985.
5. Wang S, Tachimori Y, Hokamura N, *et al*: Diagnosis and surgical outcomes for primary malignant melanoma of the esophagus: a single-center experience. Ann Thorac Surg 96: 1002-1006, 2013.
6. Sanchez AA, Wu TT, Prieto VG, *et al*: Comparison of primary and metastatic malignant melanoma of the esophagus: clinicopathologic review of 10 cases. Arch Pathol Lab Med 132: 1623-1629. 2008.
7. Mehra T, Grözinger G, Mann S, *et al*: Primary localization and tumor thickness as prognostic factors of survival in patients with mucosal melanoma. PLoS One 9: e112535, 2014.
8. Baur EH: A case of primary melanoma of the esophagus. Arb Geb Pathol Anat Inst Tubingen 5: 343-354, 1906 (In German).
9. De La Pava S, Nigogosyan G, Pickren JW and Cabrera A: Melanosis of the esophagus. Cancer 16: 48-50, 1963.
10. Volpin E, Sauvanet A, Couvelard A, *et al*: Primary malignant melanoma of the esophagus: a case report and review of the literature. Dis Esophagus 15: 244-249, 2002.
11. Bisceglia M, Perri F, Tucci A, *et al*: Primary malignant melanoma of the esophagus: a clinicopathologic study of a case with comprehensive literature review. Adv Anat Pathol 18: 235-252, 2011.
12. Ohashi K, Kato Y, Kanno J, *et al*: Melanocytes and melanosis of the oesophagus in Japanese subjects-analysis of factors effecting their increase. Virchows Arch A Pathol Anat Histopathol 417: 137-143, 1990.
13. Allen AC and Spitz S: Malignant melanoma; a clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer 6: 1-45, 1953.
14. Taniyama K, Suzuki H, Sakuramachi S, *et al*: Amelanotic malignant melanoma of the esophagus: case report and review of the literature. Jpn J Clin Oncol 20: 286-295, 1990.
15. Joob AW, Haines GK III, Kies MS, *et al*: Primary malignant melanoma of the esophagus. Ann Thorac Surg 60: 217-222, 1995.
16. Terada T: A clinicopathologic study of esophageal 860 benign and malignant lesions in 910 cases of consecutive esophageal biopsies. Int J Clin Exp Pathol 6: 191-198, 2013.
17. Kimura H, Kato H, Sohda M, *et al*: Flat-type primary malignant melanoma of the esophagus treated by EMR: Case report. Gastrointest Endosc 61: 787-789, 2005.
18. Cheung MC, Perez EA, Molina MA, *et al*: Defining the role of surgery for primary gastrointestinal tract melanoma. J Gastrointest Surg 12: 731-738, 2008.
19. Naomoto Y, Perdomo JA, Kamikawa Y, *et al*: Primary malignant melanoma of the esophagus: report of a case successfully treated with pre- and post-operative adjuvant hormone-chemotherapy. Jpn J Clin Oncol 28: 758-761, 1998.

20. Uetsuka H, Naomoto Y, Fujiwara T, *et al*: Primary malignant melanoma of the esophagus: long-term survival following pre- and postoperative adjuvant hormone/chemotherapy. Dig Dis Sci 49: 1646-1651, 2004.
21. Asakage M, Kitayama J, Tsuno NH, *et al*: Primary malignant melanoma of the esophagus treated by esophagectomy and adjuvant dendritic-cell therapy. J Gastroenterol 40: 545-546, 2005.
22. Ueda Y, Shimizu K, Itoh T, *et al*: Induction of peptide-specific immune response in patients with primary malignant melanoma of the esophagus after immunotherapy using dendritic cells pulsed with MAGE peptides. Jpn J Clin Oncol 37: 140-145, 2007.
23. Hulshof MC, Van Haaren PM, Zum Vörde Sive Vörding PJ, *et al*: Radiotherapy combined with hyperthermia for primary malignant melanomas of the esophagus. Dis Esophagus 23: E42-E47, 2010.