

PRIMARY ESOPHAGEAL MALIGNANT MELANOMA

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Primary esophageal malignant melanoma is a highly aggressive but very rare tumour. Three cases of that malignancy treated in one medical centre are presented. They were diagnosed on the basis of microscopical examination confirmed by results of immunohistochemical reactions. Metastatic melanomas of other sites were excluded clinically. The depth of esophageal wall infiltration varied from submucosa to adventitia, but lymph node metastases were observed only in one case. One postoperative death was noted. In two other patients, lung metastases were found and the patients died 20 and 16 months after surgery.

Key words: malignant melanoma, esophagus.

Introduction

Primary esophageal malignant melanoma is a highly aggressive but very rare tumour that accounts for 0.1-0.4% of all the esophageal malignancies [1]. Up to now less than 300 primary esophageal melanomas have been reported in the literature [2]. Since most reports were based on single cases or small series, little is known about genetic and molecular events that lead to development and spread of such lesions. Recently, a few genetic alterations in *NRAS*, *BRAF* and *KIT* have been found [3-5]. Furthermore, in single cases, positive immunoreaction with p53 protein, survivin and PDGFRA (*platelet-derived growth factor receptor α*) were also reported [4, 6]. Such data can be helpful for future application of new targeted therapies that can improve poor survival of patients with this malignancy.

In the current paper, clinical and morphological features of three cases of primary esophageal malignant melanomas in Caucasian patients diagnosed and treated in one medical centre are presented.

Material and methods

Three cases of primary esophageal melanoma were found in over 150 surgical esophageal specimens diagnosed during the last fifteen years (1995-2009) at the Department of Clinical Pathomorphology and treat-

ed at the 2nd Department of General Surgery, Medical University of Lublin. The skin or mucosal melanoma of other sites was excluded. In all cases, microscopic diagnosis was confirmed by immunohistochemical reactions with a panel of antibodies including HMB45, Melan A, S-100 protein, cocktail cytokeratin (MN116), epithelial membrane antigen (EMA), desmin and smooth muscle actin (SMA). All antibodies and visualization system (EnVision⁺™/HRP) were purchased from Dako (Denmark) and applied according to the manufacturer's directions.

Case descriptions

Basic data of all cases of primary esophageal malignant melanomas are presented in Table I. In cases 1 and 3, a large exophytic tumour obliterated the lumen of the esophagus (Fig. 1) giving symptoms of dysphagia [7]. In cases 1 and 2, the flat pigmented area that corresponded to melanocytosis, atypical junctional melanocyte proliferation (Fig. 2) or frank in situ melanoma was also seen. Two tumours (1 and 3) were composed of spindle-shaped and epithelioid atypical melanocytes (Fig. 3). In case 2, in which two separate lesions, i.e. gastric and esophageal were metachronously revealed, both melanomas were formed exclusively by epithelioid cells (Fig. 4 A-B) [8]. Tumours varied as far as amount and distribution of melanin are concerned.

Table I. Selected clinico-pathological features of patients with primary esophageal malignant melanoma

	CASE 1 [7]	CASE 2 [8]	CASE 3
Age (yr)	56	51	57
Sex	female	male	male
Previous medical history	unremarkable	gastric melanoma (pT1bN0Mx/R0) 67 mo before the esophageal one	unremarkable
Symptoms and signs	moderate dysphagia for 6 mo, weight loss (8 kg)	mild dysphagia	severe dysphagia for 6 mo, weight loss (20 kg), retrosternal pain
Location of the lesion(s)	28 cm from incisors	25, 32, 37 and 25 cm from incisors	middle thoracic esophagus
Gross features	pedunculated tumour and flat pigmented area	3 flat pigmented areas and 1 slightly elevated tumour	exophytic tumour
Size of the lesion(s)	3 cm × 4 cm	0.7-2 cm	7 cm
Primary histological diagnosis	benign (?) spindle cell neoplasm of muscle origin	melanoma	melanoma
Staging ^a /status of resection margins	pT2N0MX/R0	pT1bN0MX/R1 (distal margin)	pT3N1MX/R0
Treatment	tumorectomy; 5 mo later subtotal esophagectomy	subtotal esophagectomy	subtotal esophagectomy; preoperative chemo-radiotherapy
Recurrence/time	esophagus/3 mo; lung metastases/18 mo (after tumorectomy)	lung metastases/14 mo (after esophagectomy)	–
Survival	20 mo (after tumorectomy)	16 mo (after esophagectomy)	postoperative death (respiratory failure)

^aaccording to pTNM system; R0 – negative margin; R1 – microscopically positive margin; yr – years; mo – months



Fig. 1. Cross section of the large exophytic dark tumour of the esophagus (case 3)

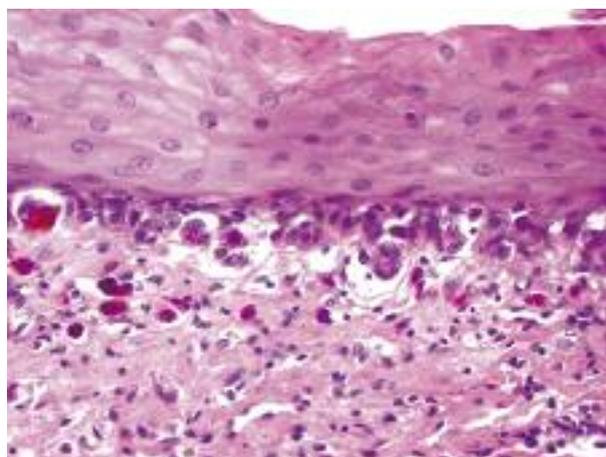


Fig. 2. An atypical junctional melanocyte proliferation within the esophageal epithelial layer (case 2). HE, objective magnification 20×

Tumour in case 1 was mostly microscopically amelanotic but in case 3, a large amount of a randomly located pigment was found both in the primary tumour and nodal metastases. All tumours were HMB45, Melan A (Fig. 5) and S100 positive, whereas other markers were

negative. The natural history of patient no. 2 was especially unusual since esophageal lesions (with microscopic features typical of the primary one) were found over five years after successful treatment of gastric melanoma.

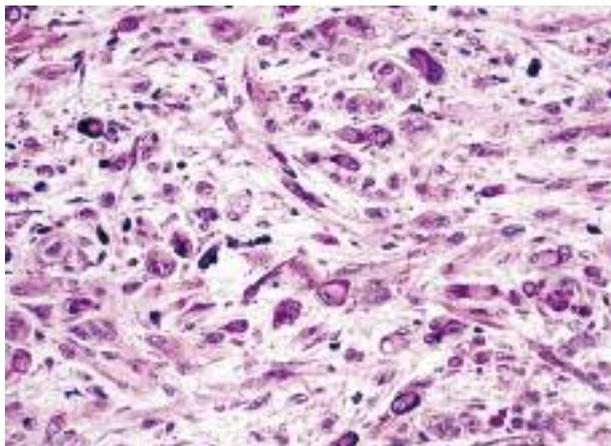


Fig. 3. Epithelioid and spindle-shaped cells of the esophageal malignant melanoma containing melanin (case 1). HE, objective magnification 20×

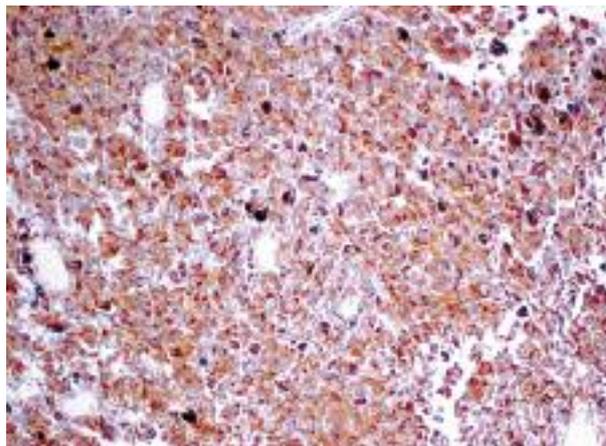


Fig. 5. Strongly positive immunohistochemical reaction for Melan A in the esophageal malignant melanoma (case 3); Dako Envision™+/HRP. HE, objective magnification 10×

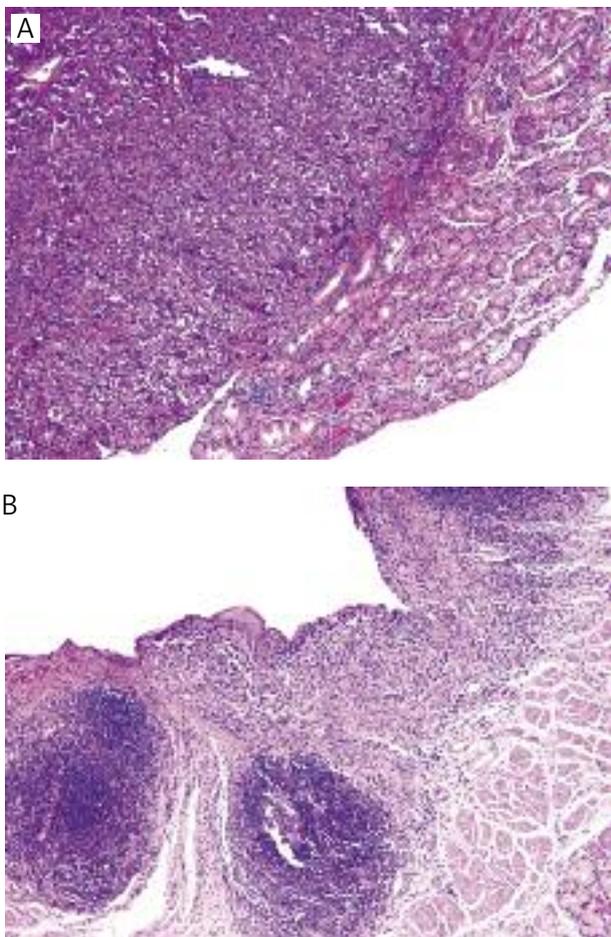


Fig. 4. Gastric (A) and esophageal (B) malignant melanomas (case 2). HE, objective magnification 5×

Discussion

The esophageal mucosa is normally devoid of melanocytes. However, due to aberrant migration of melanoblasts from the neural crest to the esophagus

during embryogenesis, they are found in 2.5-8.0% of organs [9]. An increased number of melanocytes on the epithelial-stromal junction with an increased amount of melanin is called melanocytosis or less appropriately, melanosis. This phenomenon is noted in about 13-25% of primary esophageal melanomas as well as in chronic esophagitis, squamous epithelial hyperplasia and infiltrating squamous cell carcinoma, especially in some Asian populations [9, 10]. It is supposed that melanocytosis is the consequence of proliferation of pre-existing esophageal melanocytes, scattered neuroectodermal cells or pluripotent stem cells [10]. It seems that progression from benign melanocytic lesions to atypical melanocytic proliferation precedes invasive melanoma. However, such process observed in subsequently taken endoscopic samples has been reported sporadically [11]. Nevertheless, according to the detailed study by Sanchez *et al.* [12], presence of the melanocytosis and in situ melanoma is regarded as crucial in the microscopic distinction between primary esophageal melanoma and metastatic melanoma to the esophagus. In fact, both lesions are rare and metastatic malignant melanoma to the esophagus is found just in about 4% of patients with disseminated disease at the autopsy [12].

Primary esophageal malignant melanomas developed more frequently in males (M/F = 2/1) usually in the 6-7th decade of life in the middle and the lower thoracic esophagus. At the early stage, they form an irregular pigmented area, however in time polypoid and ulcerated tumours are the most typical gross appearance of the lesions. Moreover, 85% of tumours are pigmented macroscopically [1].

In the diagnosis of primary esophageal malignant melanoma, multiple investigations are necessary [13]. Histopathological assessment of the samples taken at the upper gastrointestinal tract endoscopy seems to be crucial. However, accurate preoperative diagnosis of the

esophageal melanoma may be difficult mostly due to inadequate samples (too superficial, scanty tissue material, necrosis) or incorrect diagnosis of other malignant tumour, i.e. poorly differentiated squamous cell carcinoma, sarcomatoid squamous carcinoma, leiomyosarcoma and liposarcoma. Application of accessory methods like immunohistochemistry (visualization of antigens – HMB45, Melan A, S-100 protein, neuron specific enolase) or rarely electron microscopy (presence of melanosomes) confirmed the diagnosis [14]. Furthermore, in all cases, metastases from skin melanoma have to be clinically excluded [12].

Primary esophageal melanoma is treated by the surgery alone or adjuvant therapies [1]. The total or subtotal esophagectomy with lymph nodes dissection is the preferable mode of treatment. Despite a high percentage of nodal metastases at the time of diagnosis, melanomas are usually locally resectable [15]. More recently endoscopic mucosal resection for early lesions is also applied [16]. Real effectiveness of adjuvant therapies, i.e. radiotherapy, immunochemotherapy or hormone-based therapy is unclear due to a limited number of cases [1, 13]. After the radical esophagectomy, the mean survival is 10-14 months [17]. The 5-year survival rate was reported only in 4-37% cases [1]. Longer survival was usually achieved in patients with early stage disease [13].

Primary esophageal malignant melanoma is a rare but aggressive malignancy. Multicentre studies based on a large and representative group of patients are desirable for better understanding of biology of the tumour to establish new methods of therapy and improve survival.

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