Differentiation of a single melanocytic lesion of the esophagus : primary malignant melanoma of the esophagus or esophageal metastatic melanoma

Alexander Croo[1], David Creytens[2], Piet Pattyn[1]

(1) Department of gastrointestinal surgery, (2) Department of pathology, University Hospital and Medical School Ghent, Ghent, Belgium.

Abstract

A single melanocytic lesion of the esophagus should be differentiated from a primary malignant melanoma of the esophagus (PMME) or an esophageal metastatic melanoma (MME). This paper reviews the current knowledge about these entities and how to differentiate between them. Melanocytosis as a precursor of PMME is discussed as well. (Acta gastroenterol. belg., **2015**, 78, **327-331**).

Key words : primary malignant melanoma of the esophagus, esophageal metastatic melanoma, and melanocytosis.

Introduction

The incidence of melanoma has been increasing rapidly worldwide over the past five decades, making it the eighth most common malignancy in developed countries (1,2). However, melanocytic lesions of the esophagus remain extremely rare (2). During the past decades controversy surrounded the discussion of the existence of a primary malignant melanoma arising from the esophageal mucosa. However, multiple studies have now confirmed this hypothesis (3-6). In case of a single melanocytic lesion of the esophagus, the physician should consider a primary malignant melanoma of the esophagus (PMME) or a melanoma metastasis to the esophagus (MME). This paper gives a review of the differentiation between these entities, both on anatomopathological basis, prognosis and treatment. The possible role of melanocytosis as a precursor of PMME is discussed as well.

Embryology

In the embryonic stage, melanoblasts move away from the neural crest through peripheral nerves to the epidermis, hair follicles, oral cavity, nasopharynx, larynx, uvea, meninges and inner ear (7). Normally the esophageal mucosa is devoid of melanocytes. However, in 1963 De la Pava *et al*. (3) reported melanocytes at the mucosal-submucosal junction of the squamous epithelium of the esophagus in 4 out of the 100 normal esophagi at autopsy examination, due to aberrant migration of melanoblasts. Subsequent studies demonstrated that scattered esophageal melanocytes are present in 2,5-8% of normal esophagi. These findings clarify that malignant melanoma can occur as a primary tumor from the esophageal mucosa (4-5). Stimulated by noxious agents, like gastroesophageal reflux, these melanocytes can increase in number, resulting in a process called melanocytosis (4-5,8-9). Suggested as a precursor of primary malignant melanoma of the esophagus, Maroy and Baylac published in August 2012 the first case of melanocytosis progressing to a primary malignant melanoma of the esophagus (10).

Melanocytosis

Melanocytosis is defined as a condition of an abnormal florid melanocytic proliferation of melanocytes in the basal layer of the esophageal squamous epithelium that are positive for melanocytic markers, such as S-100, Melan-A (Fig. 1) and HMB-45 and an increased quantity of melanin in the esophageal mucosa. No signs of architectural and cytological atypia should be noticed (8-9,11-12). Although rare in Western countries, it is more common in Eastern countries, especially in India and Japan. Melanocytosis is more frequently seen in men with a men/woman ratio of 1,8/1 and tends to be present in the middle and lower third of the esophagus (11). The skin pattern of increased melanocytes in response to noxious stimuli also applies to the esophagus. It is hypothesized that melanocytosis is the result of gastroesophageal reflux disease or/and a chronic oesofagitis (4-5,8-9). Other associations include systemic diseases, like Addison disease (13), alcohol (14), anal melanoma (15) and squamous epithelial hyperplasia and infiltrating squamous cell carcinoma (11-12). While standard endoscopy only shows melanocytosis at a rate of 0,07-2,1% (5,8-9,12,15), this increases to 25-30% in a patients with PMME (16-17).

Some papers state that melanocytosis is a precursor of PMME (8-10). Only recently, a case has been described of a patient presenting with melanocytosis in 1999 with endoscopic and microscopic stable findings until 2004

Correspondence to : Prof. Dr. Piet Pattyn, M.D., Ph.D., Department of gastrointestinal surgery, University Hospital and Medical School Ghent, De Pintelaan 185, 9000 Ghent, Belgium. E-mail : piet.pattyn@ugent.be

No report of previous communication of this paper or its results. No submission to or publication in any other journal.

Submission date : 17/05/2015
Acceptance date : 05/06/2015

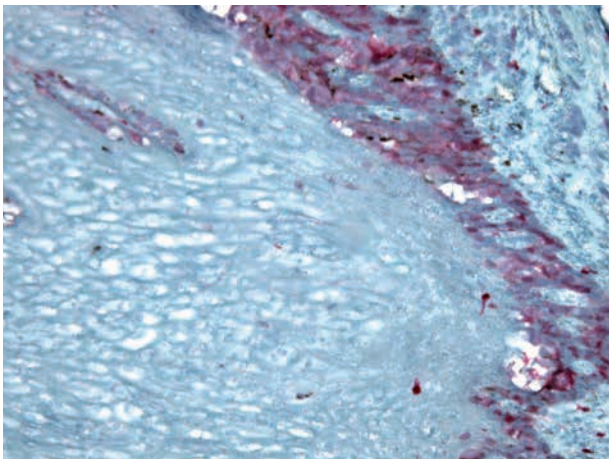


Fig. 1. — Melanocytosis. Lentiginous junctional proliferation of melanocytes, staining diffuse positive for Melan-A (400× magnification).

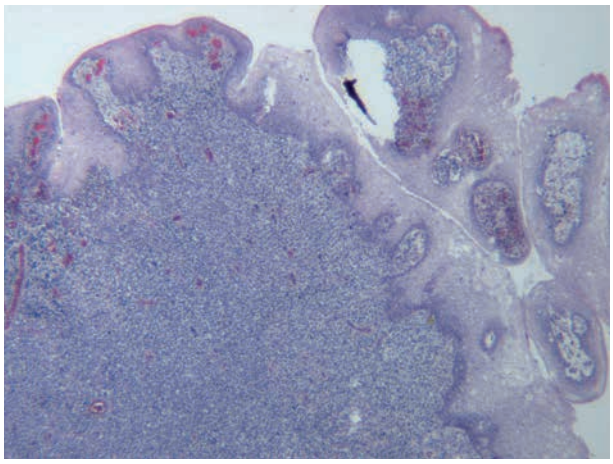


Fig. 2. — Primary esophageal melanoma (Hematoxylin and Eosin, 25× magnification). "Immunohistochemical test positive for S-100, HMB45, Melan-A and/or SOX-10".

and a diagnosis of a PMME in 2007. This is the first published case where a histological confirmed melanocytosis remains stable over a period before progressing to PMME (10). However, the oncogenesis of melanocytes remains uncertain. Melanocytosis should not be confused with melanosis, which represents an abnormal grayish black or brownish black pigmentation and is morphologically characterized by an increase in the amount of melanin in mucosal epithelial cells with or without a slight increase in the number of not atypical melanocytes (12,15). Further studies are necessary to establish and evaluate possible guidelines for the follow-up of melanocytosis. In the meantime, patients with melanocytosis should carefully be followed, even if the biopsies show no malignancy (14).

Epidemiology

Primary malignant melanoma of the esophagus was first reported by Baur in 1906 (18). This rare disease with an incidence of 0,0036 cases per million population per year is characterized by an aggressive invasion and early metastasis (11,19). Only 15% of primary melanomas are located outside the skin, with esophageal origin accounting for 0,5% (20-21). The incidence of PMME in all esophageal carcinomas is extremely low at 0,1-0,4% (16,22). Although cutaneous melanoma frequently metastasizes to the gastrointestinal tract, metastatic esophageal localization has been shown to be even more infrequently than PMME. Approximately 4% of metastasized melanomas to the gastrointestinal tract have esophageal localizations (23). Single-organ metastasis is uncommon with up to 95% of the patients with advanced metastatic malignant melanoma presenting with multiple-organ metastasis (24).

Diagnosis

Endoscopy & biopsy

Most of the esophageal melanomas are discovered by endoscopy and biopsy. However, it must be noted that they lack accuracy and do not allow a distinction between PMME and a metastatic melanoma. Endoscopically, esophageal melanoma appears as an intraluminal, lobular or polypoid, irregular and usually pigmented mass partly covered with intact mucosa (19). However, 10-25% of the esophageal melanomas present as an amelanocytic melanoma (22,25). Satellite tumor nodules, which are presumably intramural metastasis, have been reported in 12% of patients with PMME (19). Almost 90% of esophageal melanoma occur in the middle or distal third of the esophagus, probably because of the greater concentration of melanocytes in this region (16). The accuracy of a standard histological examination of a biopsy is insufficient with 20-50% of the patients being misdiagnosed as having a poorly differentiated carcinoma. This is especially the case when the melanoma cells contain either few or no melanin granules. Also the predominant submucosal localization of the tumor in more than 50% of the cases of PMME lowers the accuracy of biopsies (19). In the series of Sabanathan (19) only 54% of the patients were diagnosed preoperatively as a malignant melanoma. This mandates the use of immunohistochemical stainings to achieve a more accurate preoperative diagnosis. A diagnosis of melanoma can be made when results for S-100 protein, HMB-45, MiTF and/or SOX-10 are positive in the tumor cells (Fig. 2). Cytokeratin and CEA immunohistochemical stainings show to be negative in the tumorcells (22). Therefore, anatomopathological examination of the specimen is essential for the diagnosis of melano-

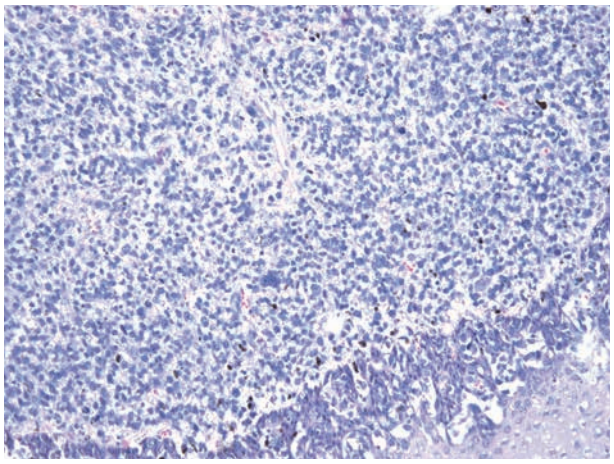


Fig. 3. — Radial (at the bottom) and vertical growth phase (above) of a primary esophageal melanoma (Hematoxylin and Eosin, 100× magnification).

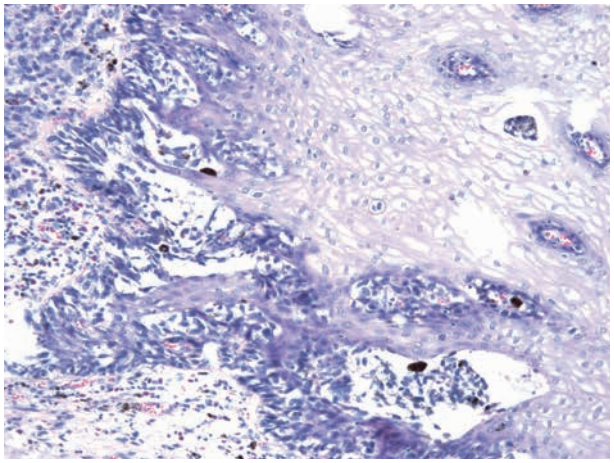


Fig. 4. — Radial growth phase of a primary esophageal melanoma showing an atypical lentiginous proliferation of single melanocytes and irregular atypical melanocytic nests at the junction (Hematoxylin and Eosin, 100× magnification).

ma, but more importantly for the distinction between PMME and MME.

Anatomopathological findings

According to the generally accepted diagnostic criteria of a primary malignant melanoma of the skin or mucous membranes, proposed by Allen and Spitz (26), malignant melanomas are considered to be primary in origin when : (i) a typical histological pattern of melanoma is found, with melanin granules inside the tumor cells and (ii) finds its origin in an area of junctional activity in the squamous epithelium. Junctional activity refers to the presence of a lentiginous proliferation of single melanocytes or melanocytic nests in the epithelium with varying degrees of architectural and cytological atypia, with in case of a melanoma in situ high-grade atypia with epidermal ascension of melanocytes (pagetoid spread).

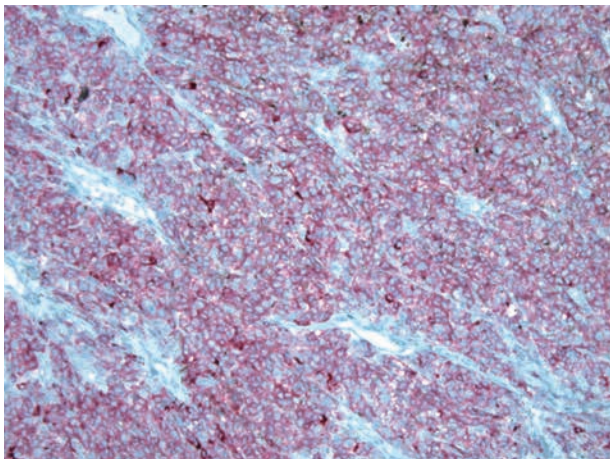


Fig. 5. — Vertical growth phase of a primary esophageal melanoma composed of invasive morphologically malignant melanocytic tumor cells staining diffusely with Melan-A (400× magnification).

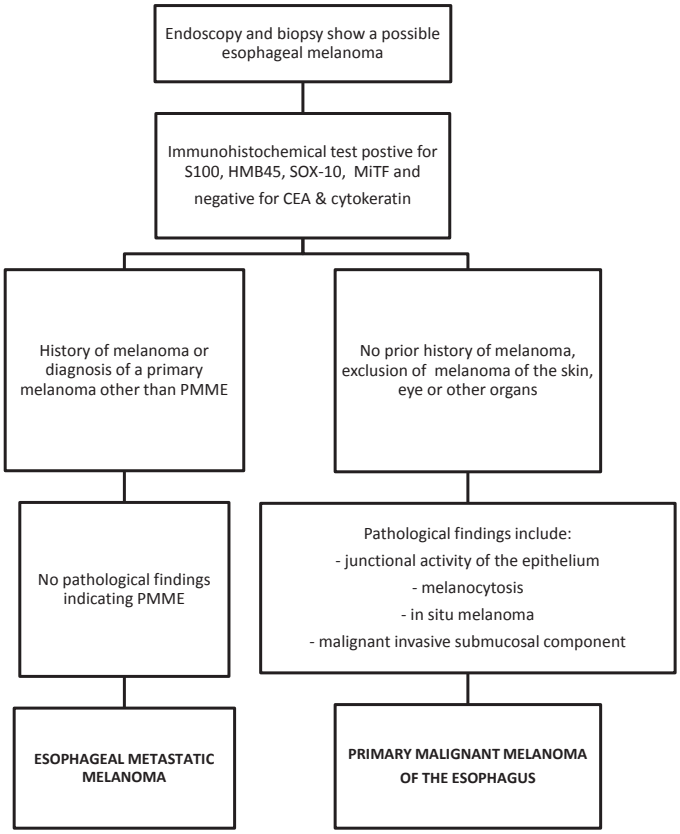
As long as there is no ulceration of the overlying epithelium, absence of junctional changes in the overlying epithelium may be interpreted as strong evidence for metastasis or recurrence (26). However, the presence of atypical melanocytic cells within the epidermis/epithelium does not completely exclude a metastasis of a malignant melanoma because rare cases of epidermotropic/epitheliotropic melanoma metastases are described in literature. In these cases strict clinicopathologic correlation is mandatory to make a correct diagnosis.

For the diagnosis of PMME, the following criteria are applicable : (i) presence of melanocytosis, (ii) in situ melanoma (radial growth phase) and (iii) a malignant invasive submucosal component (vertical growth phase) composed of morphologically malignant melanocytic tumor cells with a highly variable morphology (27) (Fig. 3, 4, 5). The finding of multiple metastasis is not in favor of metastasized melanoma, since at the time of diagnosis around 30-40% of PMME are metastasized. This includes both metastasis to regional lymph nodes like paraesophageal, celiac or supraclavicular lymph nodes and to organs including the lungs, bones and liver (19). Interestingly, while the incidence of peri-oesophageal lymph node metastasis at presentation may be as high as 66%, it is unrelated to the depth of tumor invasion (28).

When the above mentioned criteria for the diagnosis of PMME occur in the context of no prior history of melanoma and if a primary melanoma of the skin, eyes or other organs is excluded, the diagnosis of PMME is confirmed (27). Otherwise, a metastasis of a primary melanoma should be considered, necessitating careful examination of the skin, eyes and other organs covered with a mucosal membrane (flowchart).

Prognosis

Despite of an increase in the early detection of PMME in recent years, most patients present with nodal



Flowchart. — Flowchart presenting the differentiation between primary malignant melanoma of the esophagus (PMME) and metastatic melanoma of the esophagus (MME).

metastases at the time of diagnosis. Nonetheless, the resectability rate of PMME increased from 67% in the 1980's to 87% in the last decade (16). However, the mean survival of 10-13 months only increases to 14 months after esophagectomy (19,29-30). This low gain in survival can be explained because of a 77% mortality from recurrent disease occurring within the first postoperative year (16). Predictive factors of poor prognosis include age over 60 years, invasion deeper than T2, positive lymph node metastasis and positive distant metastasis (7). Five-year survival rates of PMME after surgery were originally reported to be 4.2% in 1989 (19), but a more recent study by Volpin reports a five-year survival rate of 37% (16). Approximately 85% of the patients die with disseminated disease regardless of the mode of treatment (13). The most common sites involved at autopsy are the liver (39.3%), mediastinum (34.4%), lungs (24.6%), pleura (19.7%), supraclavicular lymph node (19.7%), peritoneum (14.8%), brain (13.1%), kidneys and adrenals (11.5%), although no site is immune (16,19,29).

Regarding MME, the prognosis lowers to 6-9 months in case of a metastatic melanoma stage IV (31). Additionally, patients with a metastatic melanoma have a median age of 50 years at diagnosis, compared to 62 years in patients with PMME, lowering the life expectancy (27). This pronounced difference in prognosis between the two entities underlines the need for an accurate, preoperative diagnosis.

Treatment

For the optimal treatment strategy in patients with a melanoma of the esophagus, a PET-CT scan should be used. This technique is currently considered as the most accurate for exploring metastatic regions of a solid tumor. After consulting a PET-CT scan additional lymphadenectomy can be planned preoperatively, resulting in a better prognosis for the patient (7). Especially in case of a metastatic cutaneous melanoma, a PET-CT scan is of proven value, changing the planned treatment in up to 22% of the patients (6). In case of a unique esophageal lesion Ivor-Lewis esophagectomy is the preferential treatment in operable patients. This allows lymph node dissection and a great margin of resection, which is necessary because of the tendency of the tumor to spread longitudinally along the submucosa. The role of chemotherapy and radiotherapy in the treatment of PMME has not been establish, but the evidence of a real effectiveness is scare (7,16). When surgical resection of the tumor is not feasible, radiotherapy can be used as a palliative treatment (32). For the treatment of an advanced metastatic cutaneous melanoma new drugs have been developed. With melanoma being an immunogenic cancer,

dendritic cell based immunotherapy could be a breakthrough. Although this immunotherapy has shown to induce anti-tumor immune responses, so far only limited clinical efficacy was registered (33-34). With most of these new drugs still under evaluation in the adjuvant setting, Interferon remains the only drug of proven efficacy (35). The elucidation of the underlying molecular mechanisms of melanoma and the advent of new therapeutic options, like BRAF and MEK inhibitors, are changing the management of this tumor and offer hope for patients with advanced melanoma (36).

Conclusion

Melanocytosis is regarderd as a precursor of PMME. Therefore patients presenting with melanocytosis should closely be followed. In case of a single melanocytic lesion of the esophagus an accurate, preoperative diagnosis is essential. Biopsies should always be evaluated using immunohistochemical staining to confirm the diagnosis of a melanoma. If confirmed, PMME and metastatic melanoma can be distinguished on the basis of the medical history of the patient and the histopathological findings. If the melanoma is limited to the esophagus, Ivor Lewis esophagectomy is the preferred treatment. For the treatment of advanced melanoma, new drugs with promising results are being developed.

Acknowledgements

None of the authors report to have received financial grants or other fundings for this paper, nor do they declare to have any industrial link or affiliation.

References

1. MAC KIE R.M., HAUSCHILD A., EGGERMONT A.M. Epidemiology of invasive cutaneous melanoma. *Ann. Oncol.*, 2009, **20** Suppl 6 : vi1-7.
2. LENS M. Current clinical overview of cutaneous melanoma. *Br. J. Nurs.*, 2008, **17** (5) : 300-305.
3. DE LA PAVA S., NIGOGOSYAN G., PICKREN J.W., CABRERA A. Melanosis of the esophagus. *Cancer*, 1963, **16** : 48-50.
4. OHASHI K., KATO. Y., KANNO J., KASUGA T. Melanocytes and melanosis of the esophagus in Japanese subjects : analysis of factors effecting their increase. *Virchows Arch. A Pathol. Anat.*, 1990, **417** : 137-143.
5. YAMAZAKI K., OHMORI T., KUMAGAI Y., MAKUUCHI H., EYDEN B. Ultrastructure of esophageal melanocytosis. *Virchows Arch. A Pathol. Anat. Histopathol.*, 1991, **418** : 515-522.
6. SCHWIMMER J., ESSNER R., PATEL A., JAHAN S.A., SHEPHERD J.E., PARK K. *et al*. A review of the literature for whole-body FDG PETin the management of patients with melanoma. *Q. J. Nucleic. Med.*, 2000, **44** : 153-167.
7. IWANUMA Y., TOMITA N., AMANO T., ISAYAMA F., TSURUMARU M., HAYASHI T. *et al*. Current status of primary malignant melanoma of the esophagus : clinical features, pathology, management and prognosis. *J. Gastroenterol.*, 2012, **47** (1) : 21-28.
8. SHARMA S.S., VENKATESWARAN S., CHACKO A., MATHAN M. Melanosis of the esophagus : an endoscopic, histochemical, and ultrastructural study. *Gastroenterology*, 1991, **100** : 13-16.
9. BOGOMOLETZ W.V., LECAT M., AMOROS F. Melanosis of the oesophagus in a Western patient. *Histopathology*, 1997, **30** : 498-499.
10. MAROY B., BAYLAC F. Primary malignant esophageal melanoma arising from localized benign melanocytosis. *Clin. Res. Hepatol. Gastroenterol.*, 2013, **37** (2) : e65-e67.
11. CHANG F., DEERE H. Esophageal melanocytosis morphologic features and review of the literature. *Arch. Pathol. Lab. Med.*, 2006, **130** : 552-557.
12. WALTER A., VAN REES B.P., HEIJNEN B.H., VAN LANSCHOT J.J., OFFERHAUS G.J. Atypical melanocytic proliferation associated with squamous cell carcinoma in situ of the esophagus. *Virchows Arch.*, 2000, **437** : 203-207.
13. JONES B.H., FLEISCHER D.E., DE PETRIS G., HEIGH R.I., SHIFF A.D. Esophageal melanocytosis in the setting of Addison's disease. *Gastrointest. Endosc.*, 2005, **61** : 485-487.
14. OSHIRO T., SHIMOJI H., MATSUURA F., UCHIMA N., KINJO F., NAKAYAMA T. *et al*. Primary malignant melanoma of the esophagus arising from a melanocytic lesion : report of a case. *Surg. Today*, 2007, **37** (8) : 671-675.
15. HOROWITZ M., NOBREGA M.M. Primary anal melanoma associated with melanosis of the upper gastrointestinal tract. *Endoscopy*, 1998, **30** : 662-665.
16. VOLPIN E., SAUVANET A., COUVELARD A., BELGHITI J. Primary malignant melanoma of the esophagus : a case report and review of the literature. *Dis. Esophagus*, 2002, **15** (3) : 244-249.
17. LOHMANN C.M., HWU W.J., IVERSEN K., JUNGBLUTH A.A., BUSAM K.J. Primary malignant melanoma of the oesophagus : a clinical and pathological study with emphasis on the immunophenotype of the tumours for melanocyte differentiation markers and cancer/testis antigens. *Melanoma Res.*, 2003, **13** : 595-601.
18. BAUR E.H. Ein fall von primarem melanom des oesophagus. *Arb. Geb. Pathol. Anat. Inst. Tubingen*, 1906, **5** : 343-354.
19. SABANATHAN S., ENG J., PRADHAN G.N. Primary malignant melanoma of the esophagus. *Am. J. Gastroenterol.*, 1989, **84** : 1475-1479.
20. MILLS S.E., COOPER P.H. Malignant melanoma of the digestive system. *Pathol. Annu.*, 1983, **18** (Pt 2) : 1-26.
21. SCOTTO J., FRAUMENI J.F. JR., LEE J.A. Melanomas of the eye and other noncutaneous sites : epidemiologic aspects. *J. Natl. Cancer Inst.*, 1976, **56** : 489-491.
22. JOOB A.W., HAINES G.K. 3RD., KIES M.S., SHIELDS T.W. Primary malignant melanoma of the esophagus. *Ann. Thorac. Surg.*, 1995, **60** : 217-222.
23. DASGUPTA T.K., BRASFIELD R.D. Metastatic melanoma of the gastrointestinal tract. *Arch. Surg.*, 1964, **88** : 969-973.
24. ENG J., PRADHAN G.N., SABANATHAN S., MEARNS A.J. Malignant melanoma metastatic to the esophagus. *Ann. Thorac. Surg.*, 1989, **48** (2) : 287-288.
25. TANIYAMA K., SUZUKI H., SAKURAMACHI S., TOYODA T., MATSUDA M., TAHARA E. Amelanocytic malignant melanoma of the esophagus : case report and review of the literature. *Jpn. J. Clin. Oncol.*, 1990, **20** : 286-295.
26. ALLEN A.C., SPITZ S. Malignant melanoma : a clinicopathological analysis of the criteria for diagnosis and prognosis. *Cancer*, 1953, **6** : 1-45.
27. SANCHEZ A.A., WU T.T., PRIETO V.G., RASHID A., HAMILTON S.R., WANG H. Comparison of primary and metastatic malignant melanoma of the esophagus : clinicopathologic review of 10 cases. *Arch. Pathol. Lab. Med.*, 2008, **132** (10) : 1623-1629.
28. CALDWELL C.B., BAINS M.S., BURT M. Unusual malignant neoplasms of the esophagus. Oat cell carcinoma, melanoma and sarcoma. *J. Thorac. Cardiovasc. Surg.*, 1991, **101** : 100-107.
29. CHALKIADAKIS G., WIHLM J.M., MORAND G., WEILL-BOUSSON M., WITZ J.P. Primary malignant melanoma of the esophagus. *Ann. Thorac. Surg.*, 1985, **39** : 472-475.
30. DE MATOS P., WOLFE W.G., SHEA C.R., PRIETO V.G., SEIGLER H.F. Primary malignant melanoma of the esophagus. *J. Surg. Oncol.*, 1997, **66** (3) : 201-206.
31. TARHINI A.A., AGARWALA S.S. Cutaneous melanoma : available therapy for metastatic disease. *Dermatol. Ther.*, 2006, **19** (1) : 19-25.
32. FOGARTY G.B., TARTAGLIA C.J., PETERS L.J. Primary melanoma of the oesophagus well palliated by radiotherapy. *Br. J. Radiol.*, 2004, **77** : 1050-1052.
33. WILGENHOF S., VAN NUFFEL A.M., CORTHALS J., HEIRMAN C., TUYAERTS S., BENTEYN D. *et al*. Therapeutic vaccination with an autologous mRNA electroporated dendritic cell vaccine in patients with advanced melanoma. *J. Immunother.*, 2011, **34** (5) : 448-456.
34. BONEHILL A., VAN NUFFEL A.M., CORTHALS J., TUYAERTS S., HEIRMAN C., FRANÇOIS V. *et al*. Single-step antigen loading and activation of dendritic cells by mRNA electroporation for the purpose of therapeutic vaccination in melanoma patients. *Clin. Cancer Res.*, 2009, **15** (10) : 3366-3375.
35. ESPINOSA E., BERROCAL A., LÓPEZ MARTÍN J.A., GONZÁLEZ CAO M., CEREZUELA P., MAYORDOMO J.I. *et al*. Advances in cutaneous melanoma. *Clin. Transl. Oncol.*, 2012, **14** (5) : 325-332.
36. KIM T., AMARIA R.N., SPENCER C., REUBEN A., COOPER Z.A., WARGO J.A. Combining targeted therapy and immune checkpoint inhibitors in the treatment of metastatic melanoma. *Cancer Biol. Med.*, 2014, **11** (4) : 237-246.