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The Stage of Melanogenesis in Amelanotic Melanoma

Naoki Oiso and Akira Kawada
Department of Dermatology, Kinki University Faculty of Medicine
Japan

1. Introduction

Malignant melanoma is a tumor arising from epidermal melanocytes. It is one of the most frequently occurring malignant tumors in Caucasians. Melanoma is classified into four major primary types, superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma (palmoplantar malignant melanoma) and four minor types - subungual melanoma, mucosal melanoma, secondary melanoma from an occult primary site, and multiple primary malignant melanomas. The highly undifferentiated melanoma may produce no melanin granules. The term, amelanotic melanoma, is used loosely for both true amelanotic lesions with no pigmentation and melanomas with minimal residual pigmentation. Most cases of amelanotic melamona are metastatic, but cases of primary amelanotic melanoma have been reported.
This chapter defines amelanotic melanoma and reviews the clinical and histopathological features. This chapter also provides a basic review of melanogenesis in melanosomes in the melanocytes as well as describes the uses of immunohistochemical staining for not only diagnosing melanomas but also determining the degree of differentiation of melanoma cells. As the production of melanin granules in melanosomes is distinctly regulated from stages I to IV, immunohistochemical staining may identify the damaged step in melanogenesis, which would indicate the degree of differentiation of melanoma cells in amelanotic melanoma. This chapter is designed to improve understanding of the pathogenesis of amelanotic melanoma, which is not monogeneous but heterogenous.

2. The stage of melanogenesis in amelanotic melanoma

2.1 Amelanotic melanoma

2.1.1 The definition of amelanotic melanoma

Amelanotic melanoma is used for both true amelanotic lesions with no pigmentation and melanomas with minimal residual pigmentation (Wain et al., 2008). Recently, the term "hypomelanotic melanma" is used for melanomas with faint pigmentation (Piccolo et al., 2010; Menzies et al., 2008). The melanoma cells in amelanotic melanoma cannot produce mature melanin granules, resulting in the absence of melanin granules.

2.1.2 The clinical features of amelanotic melanoma

The absence of pigmentation is the main difficulty encountered when clinically diagnosing amelanotic melanoma (Piccolo et. al., 2008). In amelanotic melanoma, the most prevalent

clinical and histopathological type is nodular melanoma (Gualandri et al., 2009). The higher Breslow thickness of amelanotic melanoma may be associated with a worse prognosis (Gualandri et al., 2009). Amelanotic melanoma can develop from any type of melanoma, including superficial spreading melanoma (Holder et al., 1996), nodular melanoma (Kanoh et al., 2010; Oiso et al., 2010), lentigo maligna melanoma (Martires et al., 2010), acral lentiginous melanoma (Yasuoka et al., 1999), subungual melanoma (Gosselink et al., 2009; Matsuta et al., 2000), and mucosal melanoma (Khaled et al., 2009; Notani et al., 2002), as well as from primary amelanotic melanoma of the esophagus (Terada, 2009; Wang et al., 2008), cervix (Duggal & Srinivasan, 2010), and colon (Sashiyama et al., 2010).

Common clinical differential diagnoses of amelanotic or hypomelanotic melanoma may include hypomelanotic nevus, Spitz nevus, basal cell carcinoma, seborrhoeic keratosis, dermatofibroma, keratoacanthoma, pyogenic granuloma, haemangioma and Bowen's disease (Piccolo et al., 2008; Zalaudek et al., 2005; Blum et al., 2004; Ferrari et al., 2004; Zalaudek et al., 2004; Holder et al., 1996; Elmets & Ceilley, 1980).

Most reported cases of amelanotic melanoma are metastatic, but cases of primary lesions also have been described (Wain et al., 2008; Yanagi et al., 2005; Gupta & Lallu, 1997; Holder et al., 1996). Most primary cases are melanomas with minimal residual pigmentation or hypomelanotic melanoma. The depicted figure is a typical case; an 80-year-old Japanese woman having an asymptomatic bulky ulcerated nodule 20 mm in size, with slight pigmentation located peripherally on the left vulva (Oiso et al., 2010) (Fig. 1).

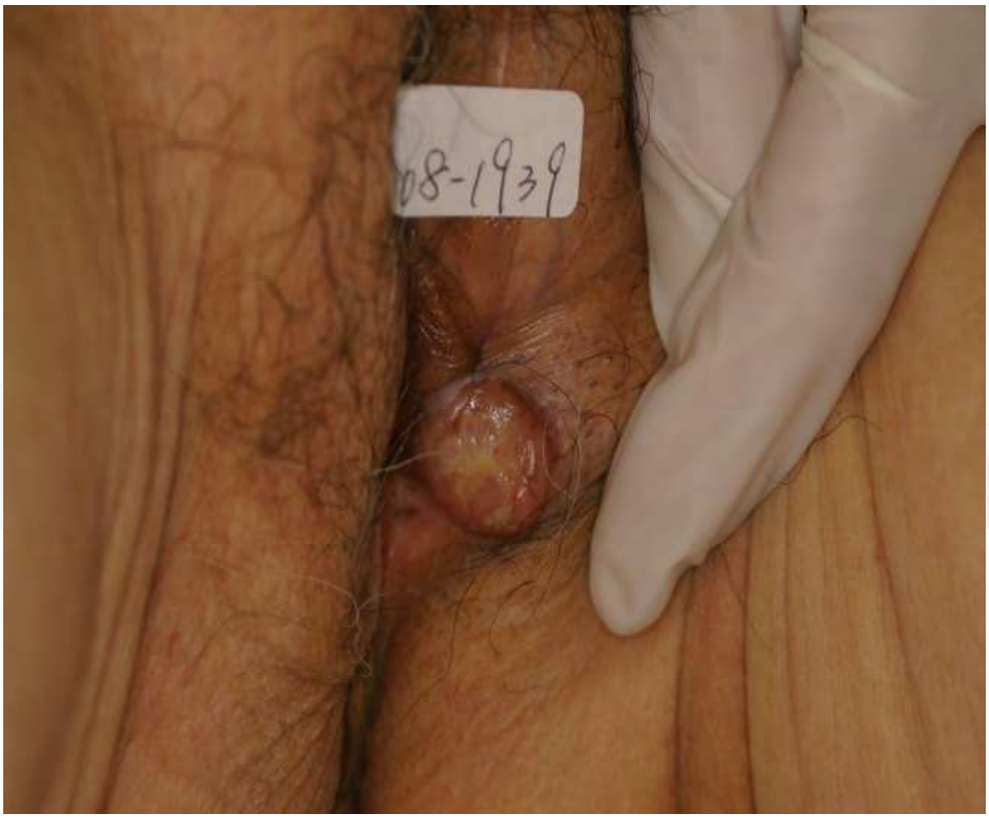

Fig. 1. An 80-year-old Japanese woman having an asymptomatic bulky ulcerated nodule 20 mm in size, with slight pigmentation located peripherally on the left vulva.

2.1.3 The histopathological features of amelanotic melanoma

Amelanotic melanoma is undifferentiated melanoma with no or few melanin granules. True amelanotic melanomas produce no melanin granules, resulting in no pigmentation, while amelanotic melanomas with minimal residual pigmentation or hypomelanotic melanomas produce a few melanin granules, resulting in some pigmentation in some part of the tumor. The histopathology of the case in Fig. 1 showed amelanotic melanomas with minimal residual pigmentation. One of the specimens had melanoma cells in the epidermis and upper dermis, with infiltration of mononuclear cells as the initial developmental lesion on the left side (Hematoxylin and eosin (HE) staining, ×100) (Fig. 2a) (Oiso et al., 2010). Massively proliferated melanoma cells were present in the dermis on the right side (Fig. 2a) (Oiso et al., 2010). The melanoma cells from the left side of the specimen had irregular shapes and large hyperchromatic nuclei with melanin granules in the upper dermis (HE, ×400) (Fig. 2b) (Oiso et al., 2010). The massively proliferated cells produced no melanin granules in the dermis on the right side (Fig. 2b) (Oiso et al., 2010). As shown here, amelanotic melanomas with minimal residual pigmentation have few melanin granules inside the tumor. However, true amelanotic melanomas have no melanin granules. The identification of melanin granules is necessary for a histopathological diagnosis of malignant melanoma other than true amelanotic melanoma.

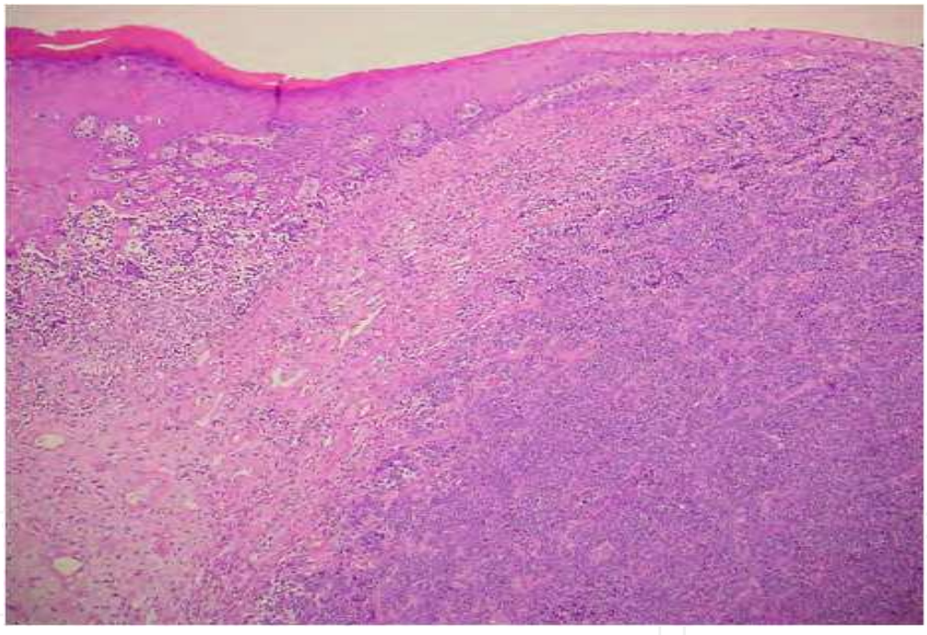

Fig. 2a. One of the specimens showed melanoma cells in the epidermis and upper dermis with infiltration of mononuclear cells as the initial developmental lesion on the left side, and massively proliferative melanoma cells in the dermis on the right side (Hematoxylin and eosinstaining (HE), ×100).

2.2 Melanogenesis in melanosomes

2.2.1The stages of melanosomes in melanocytes

Melanin granules are produced in the melanosomes in melanocytes. Each melanosome moves from the perinuclear area towards the dendrites and changes its shape from stage I to stages II, III, and IV. Stage I melanosomes (also called premelanosomes) are relatively

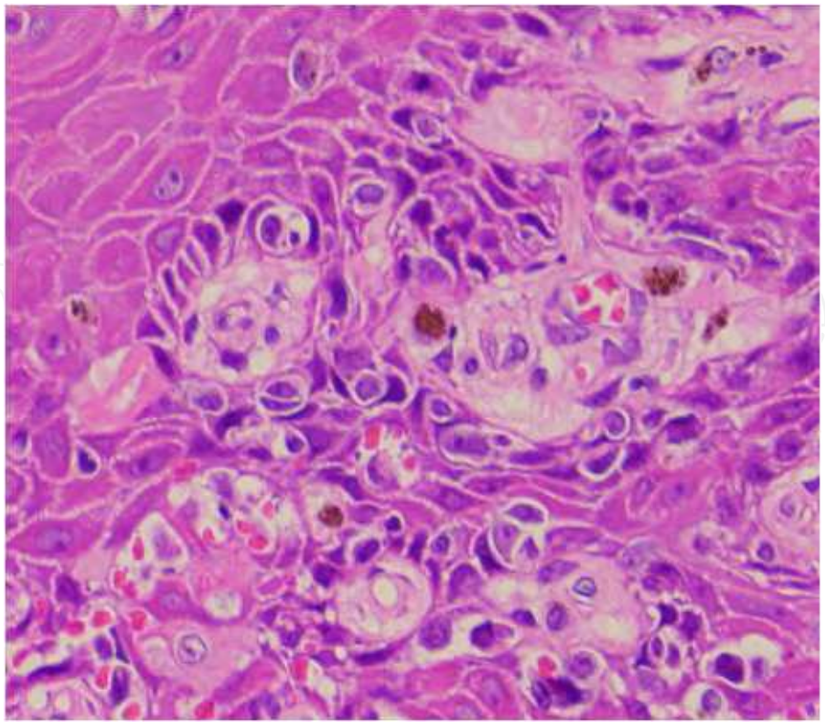

Fig. 2b. The melanoma cells from the left side of the specimen had irregular shapes and large hyperchromatic nuclei with melanin granules in the upper dermis. The massively proliferated cells in the dermis on the right side produced no melanin granules (HE, ×400).

spherical organelles with matrix material (i.e. filaments) that is beginning to assemble; stage II melanosomes are oval-shaped organelles with an organized internal matrix that does not contain melanin; stage III melanosomes are organelles with a matrix that contains deposits of melanin; and stage IV melanosomes are organelles completely filled with melanin (Boissy et al., 2006). Therefore, true amelanotic melanoma may contain stage I and/or II melanosomes, but not stage III and IV melanosomes.

2.3 Immunohistochemical staining

2.3.1 Immunohistochemical staining for diagnosis

Amelanotic melanoma is diagnosed by means of immunohistochemical staining, especially using a panel of melan-A/melanoma antigen recognized by T cells-1 (MART-1), S-100, and HMB-45 (Oiso et al, 2010). In the case shown in Fig. 1, the tumor was immunohistochemically stained with melan-A/MART-1, HMB-45, and S-100. Immunohistochemical staining with melan A/MART-1 was positive for the melanoma cells of the initially developed lesion and massively proliferated lesion (Figs. 2c, 2d) (c, ×100; d, ×400) (Oiso et al., 2010). Immunohistochemical staining with S-100 was positive for the melanoma cells of the initially developed lesion, but neative for the massively proliferated lesion except in one spot (Figs. 2e, 2f) (e, ×100; f, ×400) (Oiso et al., 2010). Immunohistochemical staining with HMB-45 was positive of for the melanoma cells of the initially developed lesion, but negative for the massively proliferated lesion (Figs. 2g, 2h) (g, ×100; h, ×400) (Oiso et al., 2010). Immunohistochemical staining is required for precisely diagnosing amelanotic melanoma.

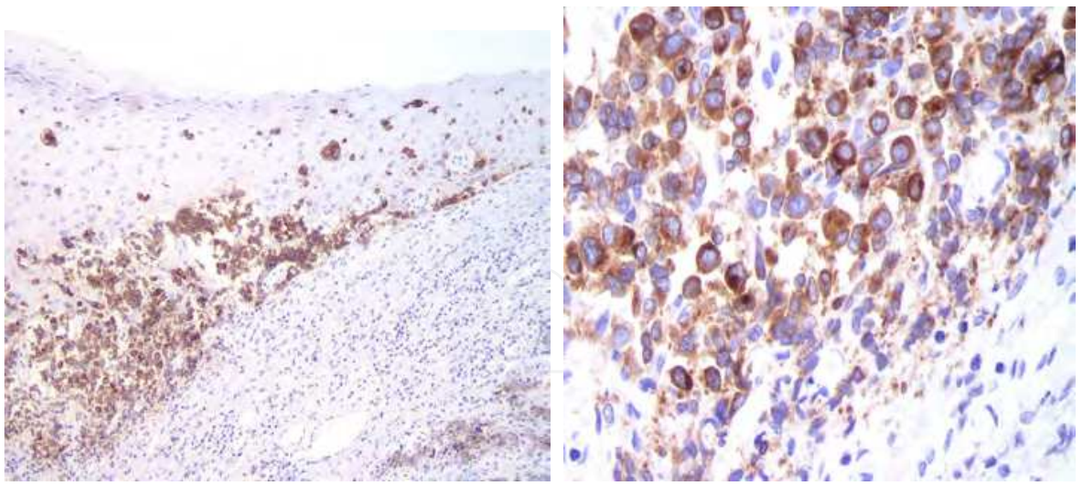

Fig. 2c-d. Immunohistochemical staining with melan A/MART-1 was positive for the melanoma cells of the initially developed lesion and the massively proliferated lesion (c, ×100, d, ×400).

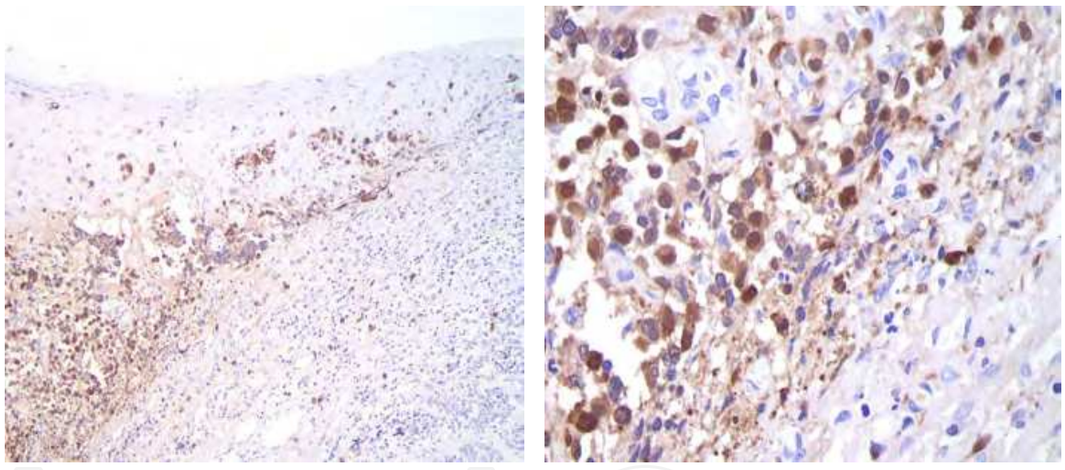

Fig. 2e-f. Immunohistochemical staining of the melanoma cells with S-100 was positive for the initially developed lesion, but negative for the massively proliferated lesion except in one spot (e, ×100, f, ×400).

Blessing *et al*. summarized the sensitivity and specificity of immunohistochemical staining using three markers for malignant melanoma: melan A/MART-1, S-100, and HMB-45 (Blessing et al., 1998). They concluded that S100 was the most sensitive marker for all primary and secondary malignant lesions and the least specific marker, that melan-A/MART-1 and HMB-45 were both highly specific, and that HMB-45 was the least sensitive of the three (Blessing et al., 1998). Several other studies have reported a similar tendency in melanin granule-producing malignant melanoma (Ohsie et al., 2008; Karimipour et al., 2004; Zubovits et al., 2003). The sensitivity of S-100, Melan-A/MART-1, and HMB-45 were 97-100%, 75-92%, and 69-93% (77-100% for primary melanomas and 56-83% for metastatic melanomas), respectively (Ohsie et al., 2008). The specificity of S-100, Melan-A/MART-1, and HMB-45 were 75-87%, 95-100%, and almost 100%, respectively (Ohsie et al., 2008).

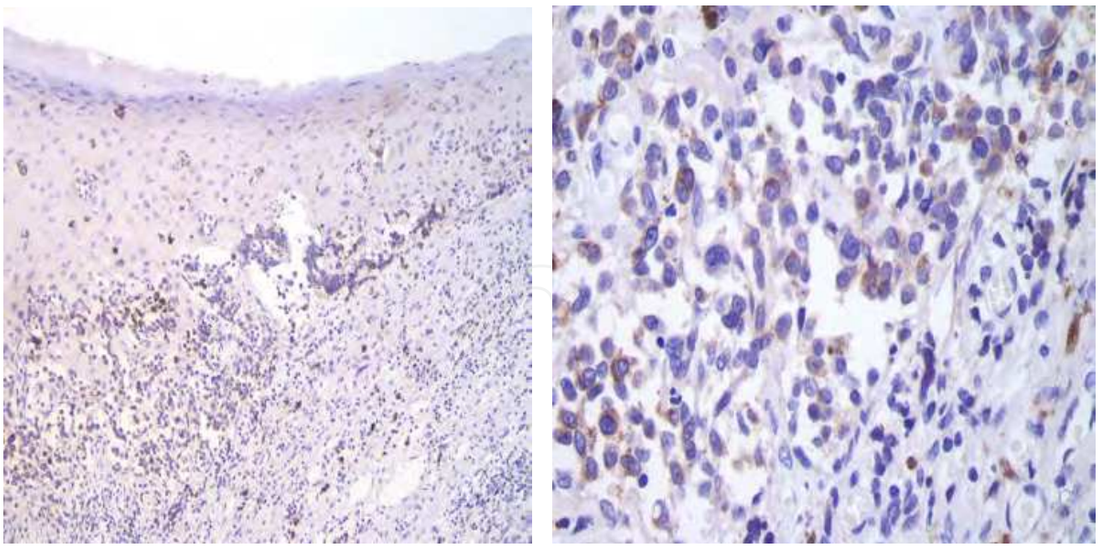

Fig. 2g-h. Immunohistochemical staining with HMB-45 was positive for the melanoma cells of the initially developed lesion, but negative for the massively proliferated lesion (g, ×100, h, ×400).

Additional candidate markers for malignant melanoma are derived from melanocytic differentiation markers, proliferation markers, immunomodulatory markers, signaling molecules, and nerve growth factors and receptors (Ohsie et al., 2008). We recommend that a tumor or a macule suspected of being a malignant melanoma be initially stained with melan-A/MART-1, HMB-45 and S-100, and, for a more precise diagnosis, secondarily stained with various markers, including microphthalmia transcription factor (MITF), tyrosine hydroxylase, tyrosinase, and tyrosinase-related proteins 1 (TRP-1) and 2 (TRP-2).

2.3.2 Immunohistochemical staining to identify the damaged step in amelanotic melanoma

Immunohistochemical stains react with the expressing and specifically modified proteins. Staining may indicate the damaged step of melanogenesis. Fig. 3 illustrates the relationship of early melanogenesis and the proteins targeted for immunohistochemical staining.

Melan-A/MART-1 is a membrane protein localized in the endoplasmic reticulum, *trans*-Golgi network, and melanosomes, especially in early melanosomes (stage I and II melanosomes) (Kawakami et al., 1994). HMB-45 specifically reacts with sialylated PMEL17/GP100 in the fibrillar matrix in the stage II melanosomes (Hoashi et al., 1996). The production of internal matrix fibers depends on the maturation and trafficking of PMEL17/GP100 (Kushimoto et. al., 2001; Hoashi et. al., 1996; Hoashi et al., 1995). In the presence of Melan-A/MART-1, PMEL17/GP100 produces melanosomal matrix fibers in melanocytes (Hoashi et al., 1995). In amelanotic melanoma, a positive reaction to both Melan-A/MART-1 and HMB-45 indicates the presence of stage I and II melanosomes; a positive reaction to only Melan-A/MART-1 indicates the presence of only stage I melanosomes. In the case shown in Fig. 1, immunohistochemical staining showed only a positive reaction to Melan-A/MART-1, indicating immature differentiation of melanosomes prior to stage II (Oiso et al., 2010).

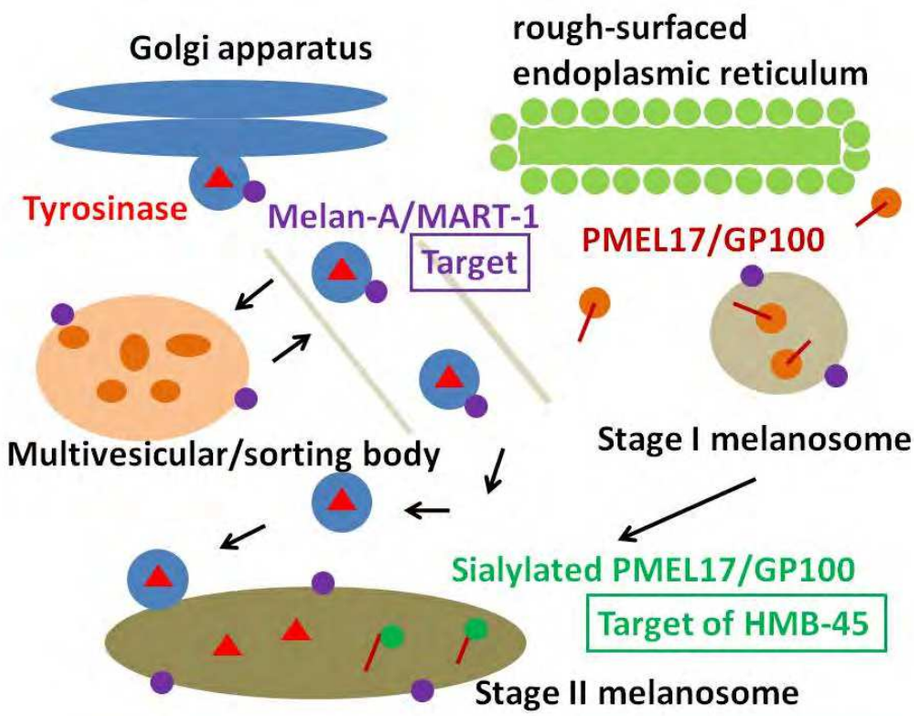

Fig. 3. The early melanogenesis in the melanocytes.

3. Conclusion

This chapter summarizes the features of amelanotic melanoma on the basis of immunohistochemical staining with melanocyte-specific proteins as targets. The results show that the damaged step in melanogenesis in amelanotic melanoma can be evaluated histopathologically. The histopathological method is useful for at least two reasons: it describes the precise pathogenesis of amelanotic melanoma with intratumor heterogeneity, and it allows the sub-classification of the damaged step in melanogenesis to be determined.

4. Acknowledgment

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5. References

Boissy, R. E., Huizing, M. & Gahl, W. A. (2006) Biogenesis of melanosomes.*in* Nordlund JJ, Boissy RE, Hearing VJ, King RA, Oetting WS, Ortonne J-P, eds: *The pigmentary system: physiology and pathophysiology*. 2nd edn. Blackwell Publishing Ltd, Oxford, pp.155-170.

Blessing, K., Sanders, D.S., Grant, J.J. (1998) Comparison of immunohistochemical staining of the novel antibody melan-A with S100 protein and HMB-45 in malignant melanoma and melanoma variants. *Histopathology* Vol.32(No.2): 139-146.

Blum, A., Jaworski, S., Metzler, G., Bauer, J. (2004) Lessons on dermoscopy: Dermoscopic pattern of hemosiderotic dermatofibroma. *Derm Surg* Vol.30(No.10): 1354.

Duggal ,R. & Srinivasan, R. (2010) Primary amelanotic melanoma of the cervix: case report with review of literature. *J Gynecol Oncol* Vol.21(No.3): 199-202.

Elmets, C.A. & Ceilley, R.I. (1980) Amelanotic melanoma as a pyogenic granuloma. *Cutis* Vol.25(No.2): 161–167.

Ferrari, A., Piccolo, D., Fargnoli, M.C., Biamonte, A.S., Peris, K. (2004) Cutaneous amelanotic melanoma metastasis and dermatofibromas showing a dotted vascular pattern. *Acta Derm Venereol* Vol.84(No.2): 164-165.

Gosselink, C.P., Sindone, J.L., Meadows, B.J., Mohammadi, A., Rosa, M. (2009) Amelanotic subungual melanoma: a case report. *J Foot Ankle Surg* Vol.48(No.2): 220-224.

Gualandri, L., Betti, R., Crosti, C. (2009) Clinical features of 36 cases of amelanotic melanomas and considerations about the relationship between histologic subtypes and diagnostic delay. *J Eur Acad Dermatol Venereol* Vol.23(No.3): 283-287.

Gupta, R.K. & Lallu, S. (1997) Cytodiagnosis of amelanotic metastatic malignant melanoma: an immunocytochemical study. *Diagn Cytopathol* Vol.16(No.3): 238-241.

Hoashi, T., Muller, J., Vieira, W.D., Rouzaud, F., Kikuchi, K., Tamaki, K., Hearing, V.J. (2006) The repeat domain of the melanosomal matrix protein PMEL17/GP100 is required for the formation of organellar fibers. *J Biol Chem* Vol.281(No.30): 21198-22208.

Hoashi, T., Watabe, H., Muller, J., Yamaguchi, Y., Vieira, W.D., Hearing, V.J. (2005) MART-1 is required for the function of the melanosomal matrix protein PMEL17/GP100 and the maturation of melanosomes. *J Biol Chem* Vol.280(No.14): 14006-14016.

Holder, J.E., Colloby, P.S., Fletcher, A., Camp, R.D. (1996) Amelanotic superficial spreading malignant melanoma mimicking Bowen's disease. *Br J Dermatol* Vol.134(No.3): 519-521.

Karimipour, D.J., Lowe, L., Su, L., Hamilton, T., Sondak, V., Johnson, T.M., Fullen, D. (2004) Standard immunostains for melanoma in sentinel lymph node specimens: which ones are most useful? *J Am Acad Dermatol* Vol.50(No.5) 759-764.

Kato, H., Inoue, Y., Ishihara, T., Kageshita, T., Ihn, H. (2010) Amelanotic malignant melanoma where primary lesion was discovered 5 years after metastasis in the lymph node. *J Dermatol* Vol.37(No.8): 730-734.

Kanoh, M., Amoh, Y., Tanabe, K., Maejima, H., Takasu, H., Katsuoka, K. (2010) Nestin is expressed in HMB-45 negative melanoma cells in dermal parts of nodular melanoma. *J Dermatol* Vol.37(No.6): 505-511.

Kawakami, Y., Eliyahu, S., Delgado, C.H., Robbins, P.F., Rivoltini, L., Topalian, S.L., Miki, T., Rosenberg, S.A. (1994) Cloning of the gene coding for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. *Proc Natl Acad Sci U S A* Vol.91(No.9): 3515-3519.

Khaled, A., Hammami, H., Fazaa, B., Kourda, N., Kamoun, M.R., Ben Jilany, S., Zoghlami, A. (2009) Primary amelanotic anorectal melanoma: an uncommon neoplasia with poor prognosis. *Pathologica* Vol.101(No.3): 126-129.

Kushimoto, T., Basrur, V., Valencia ,J., Matsunaga, J., Vieira, W.D., Ferrans, V.J., Muller, J., Appella, E., Hearing, V.J. (2001) A model for melanosome biogenesis based on the

purification and analysis of early melanosomes. *Proc Natl Acad Sci U S A* Vol.98(No.19): 10698-10703.

Martires, K.J., Capaldi, L., Pattee, S.F., Maloney, M.E., Bordeaux, J.S. (2010) Failed treatment of amelanotic lentigo maligna with imiquimod followed by pigment production. *Arch Dermatol* Vol.146(No.9): 1047-1048.

Matsuta, M., Segawa, I., Akasaka, T., Kon, S., Nara, T., Minato, S. (1990) A case of subungual amelanotic malignant melanoma: an electron microscopic study of aberrant melanosomes. *J Cutan Pathol* Vol.17(No.4): 246-250.

Menzies, S.W., Kreusch, J., Byth, K., Pizzichetta, M.A., Marghoob, A., Braun, R., Malvehy, J., Puig, S., Argenziano, G., Zalaudek, I., Rabinovitz, H.S., Oliviero, M., Cabo, H., Ahlgrimm-Siess, V., Avramidis, M., Guitera, P., Soyer, H.P., Ghigliotti, G., Tanaka, M., Perusquia, A.M., Pagnanelli, G., Bono, R., Thomas, L., Pellacani, G., Langford, D., Piccolo, D., Terstappen, K., Stanganelli, I., Llambrich, A., Johr, R. (2008) Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Arch Dermatol* Vol.144(No.9): 1120-1127.

Notani, K., Shindoh, M., Yamazaki, Y., Nakamura, H., Watanabe, M., Kogoh, T., Ferguson, M.M., Fukuda, H. (2002) Amelanotic malignant melanomas of the oral mucosa. *Br J Oral Maxillofac Surg* Vol.40(No.3): 195-200.

Ohsie, S.J., Sarantopoulos, G.P., Cochran, A.J., Binder, S.W. (2008) Immunohistochemical characteristics of melanoma. *J Cutan Pathol* Vol.35(No.5): 433-444.

Oiso, N., Yoshida, M., Kawara, S., Kawada, A. (2010) Amelanotic vulvar melanoma with intratumor histological heterogeneity. *J Dermatol* Vol.37(No.6): 537-541.

Piccolo, D., Lozzi, G.P., Altamura, D., Fargnoli, M.C., Peris, K. (2010) Dermoscopic evolution of vascular pattern in two cases of amelanotic melanoma. *Acta Derm Venereol* Vol.90(No.1): 83-85.

Sashiyama, H., Tsujinaka, Y., Hamahata, Y., Tsutsumi, O., Hoshino, T., Minami, Y., Tsunoda, Y., Yano, M., Sato, Y. (2010) Primary amelanotic malignant melanoma of the colon. *Endoscopy* Vol.42 Suppl 2: E163-164.

Terada, T. (2009) Amelanotic malignant melanoma of the esophagus: report of two cases with immunohistochemical and molecular genetic study of KIT and PDGFRA. *World J Gastroenterol* Vol.215(No.21) 2679-2683.

Wain, E.M., Stefanato, C.M., Barlow, R.J. (2008) A clinicopathological surprise: amelanotic malignant melanoma. *Clin Exp Dermatol* Vol.33(No.3) 365-366.

Wang, S., Thamboo, T.P., Nga, M.E., Zin, T., Cheng, A., Tan, K.B. (2008) c-kit positive amelanotic melanoma of the oesophagus: a potential diagnostic pitfall. *Pathology* Vol.40(No.5): 527-530.

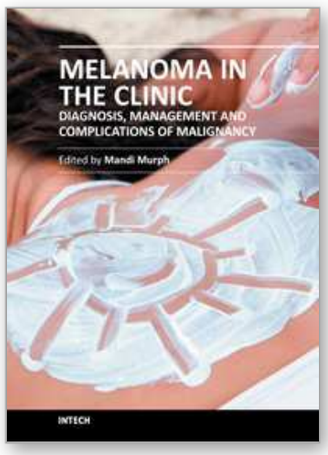
Yanagi, .T, Akiyama, M., Kasai, M., Yamakura, M., Nishio, M., Shimizu, H. (2005) Multiple skin metastases of amelanotic melanoma originating from the sinonasal mucosa. *Acta Derm Venereol* Vol.85(No.) 554-555.

Yasuoka, N., Ueda, M., Ohgami, Y., Hayashi, K., Ichihashi, M. (1999) Amelanotic acral lentiginous malignant melanoma. *Br J Dermatol* Vol.141(No.6): 370-372.

Zalaudek, I., Argenziano, G., Leinweber, B., Citarella, L., Hofmann-Wellenhof, R., Malvehy, J., Puig, S., Pizzichetta, M.A., Thomas, L., Soyer, H.P., Kerl, H. (2004) Dermoscopy of Bowen's disease. *Br J Dermatol* Vol.150(No.6): 1112-1116.

Zalaudek, I., Ferrara, G., Di Stefani, A., Argenziano, G. (2005) Dermoscopy for challenging melanoma. How to raise the "red flag" when melanoma clinically looks benign. *Br J Dermatol* Vol.153(No.1) 200–202.

Zubovits, J., Buzney, E., Yu, L., Duncan, L.M. (2004) HMB-45, S-100, NK1/C3, and MART-1 in metastatic melanoma. *Hum Pathol* Vol.35(No.2): 217-223.



Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy

Edited by Prof. Mandi Murph

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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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