

Challenges of diagnostic and treatment of metastatic acral melanoma

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Objective: to illustrate the heterogeneity of evolution and the challenges of treatment decision in cases of acral melanoma (AM).

Introduction: AM is an atypical pigmented lesion which occurs on the palms, soles and subungual surfaces¹ and it has a poorer prognosis than non-acral melanomas. This type of melanoma is rare in Caucasians and the most common location is on the lower extremities². AM has a clinical appearance that usually produces diagnostic errors and it is, particularly, more resistant to immunotherapy than other types³. Genomic studies have showed that AM has a specific mutational profile compared with other melanoma subtypes. Most of the cutaneous melanomas have BRAF or NRAS mutation, yet in AM the incidence of these alterations is lower and a large proportion fall into triple wild-type subtype⁴.

We aim to present a case of a patient with a primary BRAF positive melanoma and a secondary challenging pigmented lesion.

Results: A 70-year-old female came to the clinic with a diagnosis of an acral lentiginous melanoma, stage pT3bN1M1 (Breslow thickness of 1.7 mm), localised on the plantar aspect of the right foot, for further evaluation. The patient had secondary determinations in the right external iliac lymph nodes and multiple loco-regional metastases on the right plantar area and perimalleolar region (Fig 1). The tumor was BRAF positive, therefore the patient received systemic therapy with Dabrafenib/ Trametinib for almost a year. Under this treatment the metastases diminished in size and number, but after a few months a new pigmented lesion developed right next to the excision scar of the primary melanoma (Fig. 2).

Histopathological result indicated acral lentiginous melanoma, BRAF negative, maximal thickness on biopsy 1.5mm. At this point two possibilities were discussed: a new metastasis with loss of BRAF mutation, or a new primary melanoma BRAF negative. The systemic therapy was switched to Nivolumab. Imaging investigations (chest CT scan, head, abdominal and pelvic MRI) were negative for systemic metastases. Blood tests: protein S100, LDH, CEA were all within the normal range. During the therapy with Nivolumab the cutaneous metastases continued to progress, growing in number and size, but losing their melanocytic pigment (Fig.3). The growth in size was confirmed by histopathology as of neoplastic nature, BRAF positive, and not of inflammatory reactive type.

As local therapeutical options as electrochemotherapy, T-VEC, isolated limb perfusion⁵ were not available in Romania and the upgrade from Nivolumab to combination Nivolumab + Ipilimumab was also not allowed by Romanian protocols, it was decided to switch the therapy to Ipilimumab monotherapy (Fig. 4,5). Local radiotherapy (RT) was associated. Due to systemic progression (pulmonary metastases) Ipilimumab was discontinued after 4 doses and replaced with Dacarbazine (DTIC). As per 09/2020 the patient has clear regression of cutaneous metastases and has completed 6 months of DTIC.



Fig. 1 Cutaneous metastases of the first melanoma



Fig. 2 The second melanoma



Fig. 3 Evolution of the metastases



Fig. 4,5 Progression under Ipilimumab



Fig. 6,7,8 Regression at 3,6 and 7 months after RT respectively at 1,4,5 months of DTIC

Discutions:

A particularity of this case is the heterogeneity of the tumoral populations, with coexistence of BRAF positive and negative tumors. Also, it illustrates a challenging differential diagnosis between heterogeneous metastases with different mutation profile and secondary primary tumors. Moreover, this case exhibits an unpredictable evolution of the metastatic melanoma. It had a poor response to immunotherapy, although with a longterm, slow, local only progression without systemic extension of the metastases, but a good response to radiotherapy. It also highlights the shortcomings in availability and protocols of innovative therapy still existing in Eastern European countries. Giving the complex situation of the patient (heterogeneous mutational status, lack of response to immunotherapy, limited local therapy options), the stringent question remains how to best continue this patient's treatment.

REFERENCES:

1. <https://www.visualdx.com/visualdx/diagnosis/acral-lentiginous-melanoma?moduleId=101&diagnosisId=53033>
2. Acral lentiginous melanoma: a single-center retrospective review of four decades in East-Central Europe. Csányi I, Houshmand N, Szies M, Ócsai H, Kemény L, Oláh J, Baltás E. J Eur Acad Dermatol Venereol. 2020 Jan 27.
3. Anti-PD-1 and Novel Combinations in the Treatment of Melanoma—An Update; Frank Friedrich Gellrich, Marc Schmitz, Stefan Beissert and Friedegund Meier. J. Clin. Med. 2020, 9, 223;
4. Melanoma subtypes: genomic profiles, prognostic molecular markers and therapeutic possibilities. Roy Rabbin, Peter Ferguson, Christian Molina-Agular, David J Adams, Carla D Robles-Espinoza. J Pathol. 2019 Apr; 247(5): 539-551.
5. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. O. Michielin, A. van Akkooi, P. Ascierto, R. Dummer & U. Keilholz, on behalf of the ESMO Guidelines Committee.