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LETTER TO THE EDITOR

# Melanoma metastases occuring 40 years after primary melanoma

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Late recurrence of cutaneous melanoma is defined as the onset of metastases more than 10 years after primary melanoma diagnosis [1]. Although its incidence is low, this event is not so rare, even after many years [1,2].

Cutaneous melanoma can develop loco-regional and/or distant metastases in 20% of cases [1,2]. Although most of melanoma recurrences (65–81%) will occur within 3 years after treatment, metastases can also occur after 10 years [3]. The frequency of this event varies from 1.1 to 6.9% of melanoma patients [1,4,5]. Recurrence rates using actuarial analysis were reported to be 6.8 and 11.3%, after 15 and 25 years, respectively, for those patients disease-free for 10 years or more [4]. Instead, late metastases are more common for uveal melanoma, with relapse disease rates of 34% [5].

About 70% of newly diagnosed melanoma today are thin tumors which present a good prognosis [6–8]. However, thin melanoma patients, particularly with high risk factors

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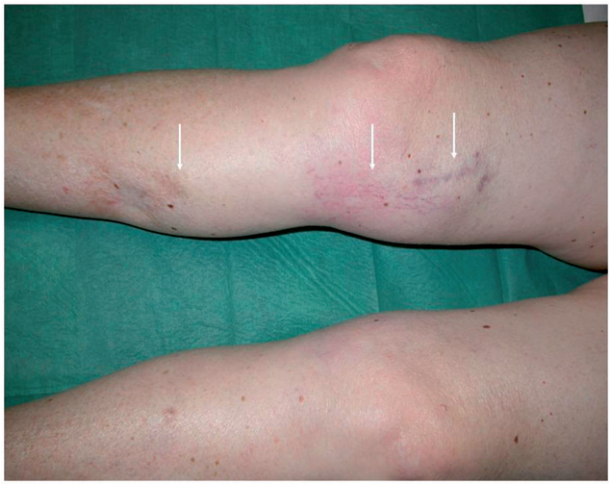

Figure 1. Subcutaneous nodules located on the inner surface of the right limb.

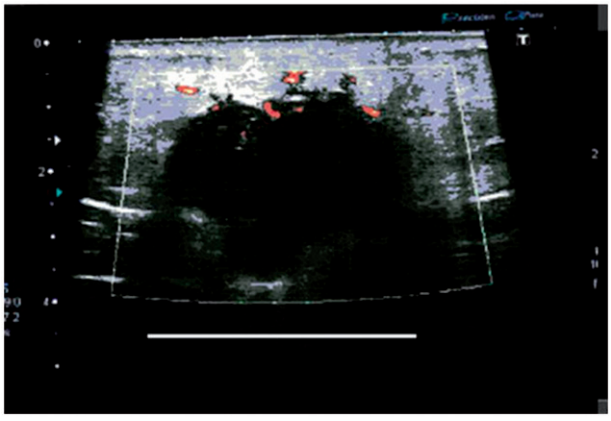

Figure 2. An US image of the thigh lesion, confirming the presence of a hypoechoic, vascularized nodule.

(ulceration and/or mitotic rate $\geq 1/mm^2$), seem to be prone to develop late recurrences [4,6]. We describe an unusual case of melanoma metastases appearing 40 years after primary cutaneous melanoma excision.

## Case presentation

At the end of 2012, an 80-year-old woman was referred to our center for the sudden onset of three subcutaneous nodules on her right limb.

Her clinical history revealed that she had a melanoma on the right leg that was surgically excised 40 years before. The histology report revealed a superficial spreading melanoma (Breslow thickness 0.5 mm and Clark level II). Since then she carried out regular follow-up, until she decided to stop 15 years ago. Clinical examination revealed the presence of three subcutaneous nodules located on the inner surface of the right limb (Figure 1).

An ultrasound (US) examination revealed the presence of three highly vascularized hypoechoic nodules (Figure 2). The histology of a US-guided fine needle biopsy of one lesion confirmed the presence of melanoma spindle cells (S100+). Total whole-body computed tomography (CT) scanning with

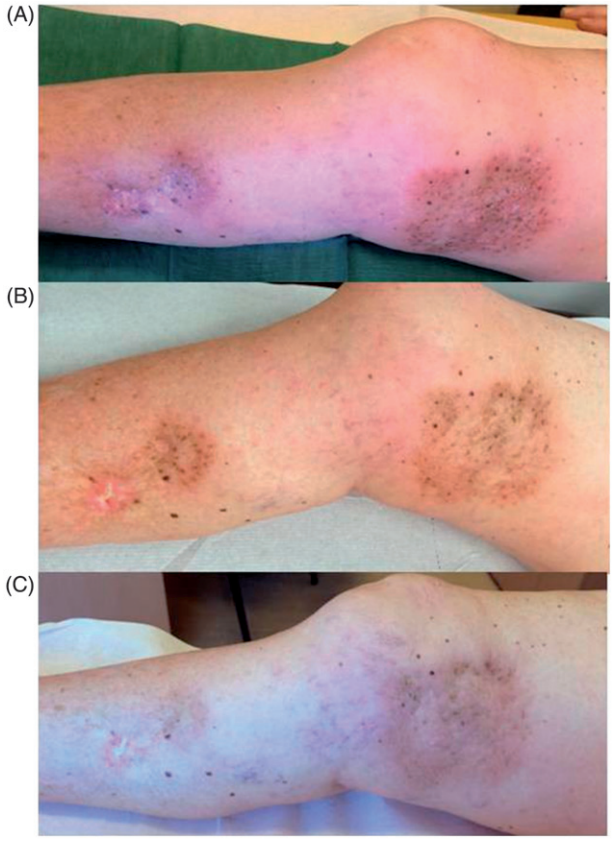


Figure 3. Leg lesions at follow-up after 1 (A), 2 (B) and 3 (C) months from the second ECT treatment.

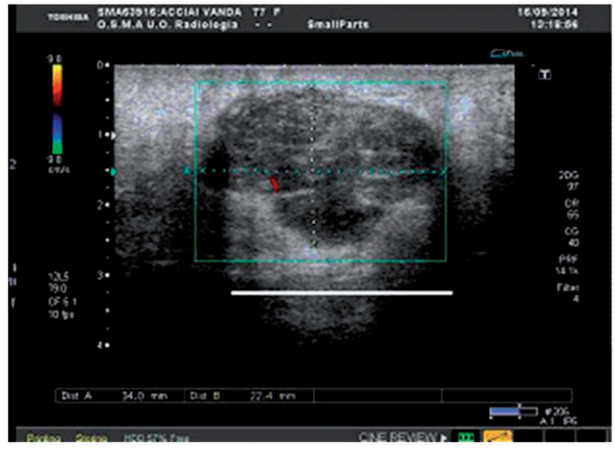

Figure 4. An US image of the thigh lesion seen in Figure 2, confirming the presence of an hyperechoic lesion with almost no vascular component.

contrast medium was negative, while a positron emission tomography (PET)-CT resulted positive in all the lesions of the limb. The patient refused both demolitive surgery and limb perfusion therapy, so we opted for intra-arterial infusion therapy with dacarbazine and cisplatin (six cycles). As skin lesions were not completely regressed after local chemotherapy, we decided to treat the patient with electrochemotherapy (ECT) (bleomycin 15,000 UI/$m^2$).

Three months after the treatment, the lesions showed a partial response. Consequently, a second ECT treatment was performed. After further 3 months, a complete clinical regression of the lesions was observed. (Figure 3). The regression

was also confirmed by US, with the presence of hyperechoic lesions with almost no vascular component on the right limb (Figure 4). After 6 months, a new CT re-staging revealed the onset of a 17-mm hypodense nodule within the right lobe of the thyroid gland. An US-guided biopsy of the nodule confirmed the presence of melanoma cells.

The *BRAF* gene mutation test revealed that it was a V600E-mutated melanoma. Target therapy with dabrafenib was started and, after 6 months, a whole-body CT showed a regression of the thyroid nodule and no other systemic signs of melanoma metastases. After further 6 months, a total body CT was negative and the patient decided to stop the therapy. To date, the patient is in good health conditions without clinical and/or instrumental signs of melanoma recurrence.

## Discussion

We report an unusual case of melanoma metastases, occurring 40 years after primary tumor excision. To the best of our knowledge, this is the first case reporting melanoma metastases 40 years after skin tumor diagnosis. An additional uncommon aspect is the presence of melanoma metastases in the thyroid gland which represents a very rare event [2,7].

The established literature on late recurrence varies from 1.1 to 6.9% of melanoma patients [1,4]. Moreover, late recurrences have been associated with both tumor (thin melanomas) and patient (younger age, female predominance) characteristics [3] and, even if, they are predominantly distant metastases, they are usually associated with a better post-recurrence survival [4].

The concept of tumor dormancy may explain late recurrences. This phenomenon is well described in several malignancies, including melanoma and it is defined as 'a period in cancer progression in which residual disease is present, but it remains asymptomatic' [1].

Metastatic cells could implant in different organs and remain dormant for years thanks to a 'balance' between the host immune system and melanoma cells [1]. Alterations of this balance might lead to melanoma cell proliferation and clinical relapse.

Since most of the recurrences occur within 3 years from the diagnosis [3] or at the latest within 10 years [8], the frequency of follow-up is usually reduced, or even interrupted, after a decade. That is why the surveillance of patients after 10 years from initial diagnosis is problematic, and duration and type of follow-up protocol is still a matter of debate. Surveillance has been shown to improve life-expectancy, but not to reduce mortality rate [3].

The prognosis of metastatic melanoma is poor, with median survival for metastatic melanoma ranging from 2 to 12 months [2]. However, the advent in the last years of innovative therapies, such as immunotherapies and targeted therapies, have significantly changed the expectancies. Immunotherapy approach, based on monoclonal antibodies able to inhibit the immune system checkpoints (anti CTLA-4 and anti PD-1), overcomes the tolerance towards tumor-associated antigens [9]. BRAF gene mutations, present in approximately 50% of cutaneous melanoma, lead to the development of the so-called 'targeted therapy' with significant results in treating metastatic melanoma [9].

## Conclusions

Growing evidence suggests that combination of loco-regional and systemic therapies may lead to synergistic anti-tumor effects in advanced melanoma, stressing the importance of a multidisciplinary approach in the treatment of these patients [10,11].

Our case shows that cutaneous melanoma can relapse at any time, even after 40 years from the initial diagnosis, and this should always be considered when dealing with melanoma patients. Although distant metastases are often associated with limited survival, a prompt diagnosis and a proper multidisciplinary approach and combination therapy can control the disease progression.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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