Eur J Dermatol 2015 (epub ahead of print)

CORRESPONDENCE

Complete regression of melanoma skin metastases after electrochemotherapy plus ipilimumab treatment: an unusual clinical presentation

Skin metastases represent a relatively frequent event in the natural history of melanoma, developing both in early and in late disease stages. Cutaneous or subcutaneous lesions arise in 15-20% of patients; almost 50% of subjects with metastatic disease have soft tissue metastases [1]. The treatment of these lesions is still a challenge: surgical excision and radiotherapy represent the standard treatments for isolated lesions, while melphalan and/or tumour necrosis factor limb perfusion is considered the standard of care for multiple lesions involving the entire extremity [2]. Electrochemotherapy (ECT) represents an effective therapeutic option, both for first-line treatment and in palliative settings, especially in painful and bleeding lesions [3, 4]. ECT, by means of brief and intense electric pulses, increases the cell membrane permeability to anticancer drugs (such as bleomycin and cisplatin) that normally scarcely penetrate into the cells. More recently, the novel systemic drugs approved in the treatment of advanced melanoma (e.g. the anti-CTLA-4, PD-1 /PD-1L blockers and the MAP kinase inhibitors) also showed a clinical benefit in the treatment of patients affected by cutaneous metastases [5].

Herein we describe a case of an advanced melanoma in which a sequential treatment with ECT plus ipilimumab induced a complete clinical response of multiple cutaneous metastases, with unusual vitiligo-like lesions as the final outcome.

A 71-year-old Caucasian male had a prior excision of a pT2b malignant melanoma located on his left leg in December 2010; sentinel lymph-node biopsy resulted negative. After two years, he developed multiple bluish papulo-nodular metastatic lesions ranging from 0.5 to 1.5 cm, on the same limb *(figure 1A)*. The clinical scenario was suggestive for in-transit melanoma metastases. FDG PET/CT scan confirmed the high metabolic activity and excluded visceral involvement. During an eight-month period, three ECT treatments were performed with 15mg/m^2 intravenous bleomycin, using the Cliniporator TM device (IGEA Ltd, Carpi, Italy). Neither post-treatment complications nor peripheral nerves injuries, nor post-procedural pain were observed. Globally, 28 lesions were treated, with a partial response *(figure 1B)*. The scheduled total body CT-scan, performed three months after the last ECT session, revealed multiple liver and adrenal glands metastases. Thus ipilimumab treatment at the standard dose of 3 mg/kg was

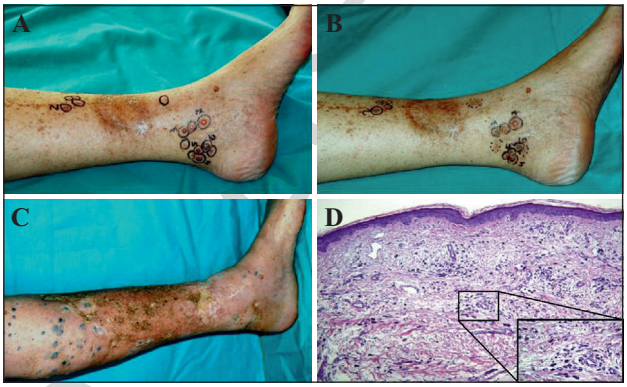

Figure 1. A) multiple bluish papulo-nodular metastatic lesions ranging from 0.5 to 1.5 cm in diameter on the left leg. **B)** cutaneous lesions after three ECT. **C)** Multiple vitiligo-like hypopigmented lesions on the sites of previous cutaneous metastases, persistent one year after the end of the ipilimumab treatment. **D)** post-inflammatory dermal melanosis at the histopathological analysis.

administered; no immune-related adverse events were reported. One month after the end of the anti CTLA-4 treatment we observed a progressive reduction in diameter, thickness and pigmentation of the cutaneous lesions; vitiligo areas became visible around the ECT treated lesions. A complete (visceral and cutaneous) response was confirmed by a PET/CT scan. Two skin biopsies in the site of prior metastatic lesions revealed only a post-inflammatory dermal melanosis *(figure 1C)*. One year later the patient still has a durable complete response with multiple vitiligo-like hypo-pigmented lesions *(figure 1D)*.

Melanoma is an immunogenic cancer characterized by the presence of tumor-infiltrating lymphocytes that justify the clinical responses to immunotherapy. Tumor-associated antigens (TAAs), recognized by autologous antibodies and T-cells and capable of inducing tumor-directed immune responses, were identified in melanoma earlier than in other tumors. Studies of the nature of these interactions led to the development of many immunotherapeutic strategies; one immunotherapeutic anti-CTLA-4 agent, ipilimumab, was recently approved for the treatment of metastatic melanoma [5]. Roux *et al.* demonstrated that, after ECT antigen-presenting cells are recruited in the treated area, the expression of toll-like receptor 9 is up-regulated [6]. A recent study by Gerlini *et al.* [7] provides the rationale for combining ECT with dendritic cell (DC) activation protocols in a clinical setting. Their results confirm that ECT produces an inflammatory infiltrate with a high number of DCs and that cell-death induced by ECT releases TAAs [8]. DC recruitment and TAA availability are two essential

doi:10.1684/ejd.2015.2522

To cite this article: Brizio M, Fava P, Astrua C, Cavaliere G, Savoia P. Complete regression of melanoma skin metastases after electrochemotherapy plus ipilimumab treatment: an unusual clinical presentation. *Eur J Dermatol* 2015 (epub ahead of print) doi:10.1684/ejd.2015.2522

factors in systemic antitumor immunity. More recent findings suggest that the combination of ECT with immunotherapy may produce an effective immune response for systemic tumor control [9].

In our case, the onset of vitiligo-like lesions, developed exclusively around the site of previous ECT, might suggest the presence of an enhanced localized immune-activation, as a consequence of increased TAA liberation on ECT treated lesions. On the basis of this observation, even if the role of ipilimumab alone cannot be excluded, we postulate a combined role of ECT and ipilimumab and suggest that the complete response observed may be expression of an abscopal effect, similar to that observed in other therapeutic associations involving ipilimumab and radiotherapy [10]. If these observations are confirmed on larger clinical studies, the local response triggered by ECT might be used to enhance a systemic response in advanced melanoma patients treated with ipilimumab. ■

Disclosure. *Financial support: none. Conflict of interest: none.*

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doi:10.1684/ejd.2015.2522

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