Skin Necrosis Revealing Antiphospholipid Syndrome During Immunotherapy for Melanoma

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Immunotherapeutic approaches have been developed recently for the treatment of advanced melanoma, based on the finding that the immunological response to melanoma plays a key role in control of the disease (1). We report here a case of a patient with metastatic melanoma who developed antiphospholipid syndrome (APLS) after initiation of immunotherapy.

CASE REPORT

In December 2006, a 53-year-old man presented with toe discoloration and subungueal haemorrhages. Fifteen years previously (in 1991) he had been diagnosed with a superficial spreading melanoma of the left thigh, 4 mm in thickness, Clark's level IV. During follow-up, the patient presented with four successive involvements of regional lymph nodes, requiring lymphadenectomy. In April 2002, pre-operative blood tests had revealed a prolongation of the partial thromboplastin time test (PTT), with a 1.31 ratio (normal range < 1.2) and autoantibodies consistent with a lupic anticoagulant. The patient was negative for antiphospholipid (APL) antibodies, negative for rheumatoid factor, but positive for antinuclear antibodies at a titre of 1/160. In April 2006, computerized tomography (CT) revealed a lymph node of 14 mm in the external left iliac area. Histological analyses revealed the presence of metastasis.

The patient received six subcutaneous injections of mature dendritic cells pulsed with lysates of three melanoma cell lines from 3 August to 11 October 2006, followed by subcutaneous pegylated interferon-alpha-2b (PEG-IFNα 2b) (1.5 µg/kg/week) from 5 August to 15 November 2006 (Fig. 1). In October 2006, a new CT scan revealed bilateral enlargement of lymph nodes in the iliac and inguinal areas, but lymphadenectomy showed no metastasis. Six days later, cyanotic and hyperaesthesic lesions appeared on the first left toe, followed by spreading of bilateral purpuric, necrotic areas and erythematous, purple painful macules to the other toes (Fig. 2A), and subungueal splinter haemorrhages appeared on both hands (Fig. 2B). Doppler ultrasonography demonstrated a deep vein thrombosis at the junction between the left external iliac vein and the left common femoral vein, and occlusion of the right radial artery. Biological parameters were: white blood cell (WBC) count 10×10^9/l (lymphocytes: 6.6%, neutrophils: 83.5%), platelet count 359×10^9/l, haemoglobin level 11.2 g/dl. The PTT was more than twice the normal rate (ratio: 2.27) and elevated levels of IgG anticardiolipin antibodies (IgG: 60 IU/ml, normal < 15) were detected, leading to the diagnosis of APLS. Antinuclear antibodies were present at 1/320 with a speckled pattern, rheumatoid factor was positive (19 U/ml, normal < 10) and anti-thyroglobulin was also slightly positive (1.4 MU/l, normal < 1). A skin biopsy on the left toe demonstrated ischaemia and thrombosis of small-sized superficial vessels of the dermis (Fig. 2C). These findings were all consistent with the diagnosis of APLS (2). The patient

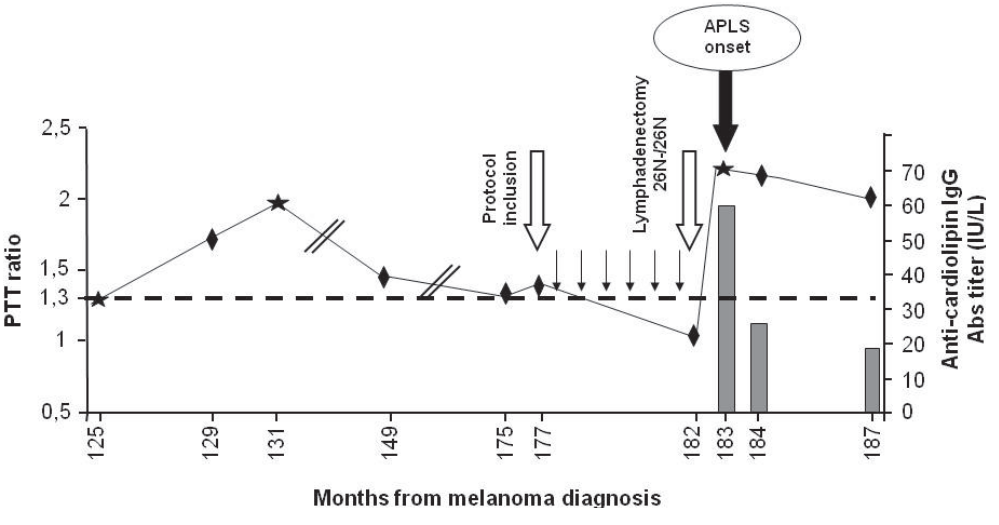

Fig. 1. Evolution of the partial thromboplastin time (PTT) ratio and antiphospholipid syndrome involvement during the course of melanoma. The number of months from initial diagnosis of melanoma is indicated. Black arrows (↓) indicate the six injections of vaccine, while pegylated interferon-alpha-2b was given every week (1.5 µg/week/kg) from time of inclusion. *Diamonds*: PTT value; *stars*: detected lupus anticoagulant; *grey histograms*: anticardiolipin immunoglobulin G antibodies titres (IU/l) detected by enzyme-linked immunosorbent assay.

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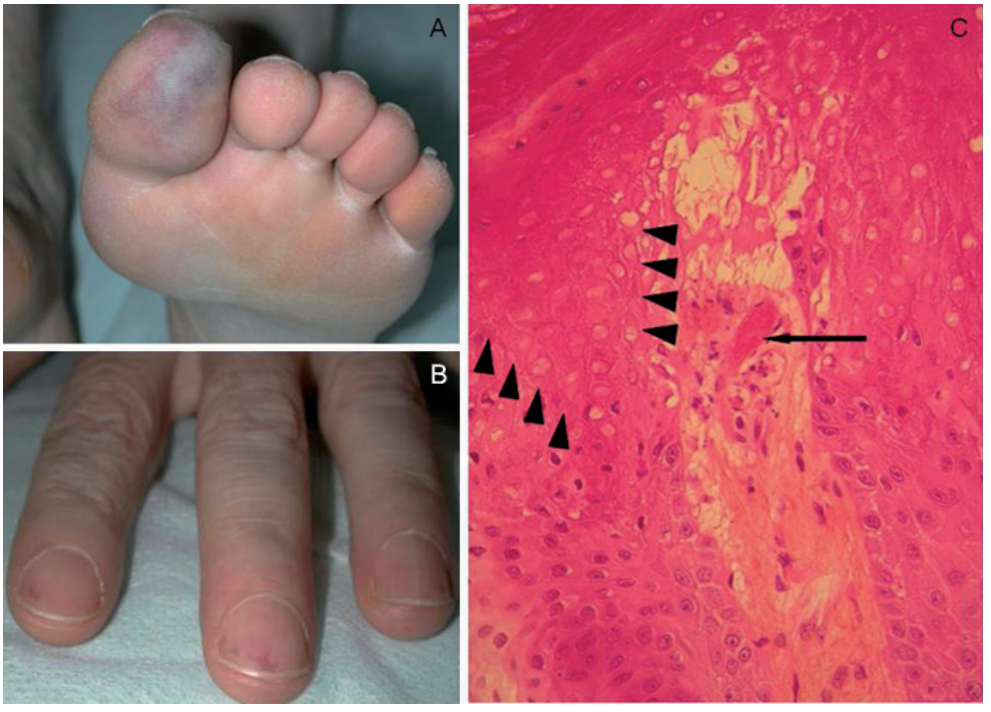

Fig. 2. Clinical onset at time of antiphospholipid syndrome (APLS) diagnosis. Acrocyanosis and purpuric lesions of the feet spread with cyanotic and necrotic lesion of (A) the first left toe, while (B) subungueal splinter haemorrhages were present on both hands. (C) A skin biopsy of the left toe showed widespread necrosis of the epidermis (*arrowheads*) and an occlusive luminal thrombus (*arrow*) of a small sized-vessel in the upper dermis, with necrosis of the vessel walls. These findings were consistent with the diagnosis of APLS.

recovered fully after treatment with heparin followed by oral anticoagulants and calcium antagonists and the serum levels of IgG anticardiolipin antibodies concomitantly and gradually decreased to 18 IU/ml.

DISCUSSION

APLS has been reported previously in melanoma patients treated with IFN-α alone or combined with interleukin-2 (3). Melanomas may also lead to the development of autoimmunity, and specifically to the appearance of APL antibodies. In a review of all cases of malignancies associated with APL antibodies, melanoma was reported in 5% (4). The development of autoimmunity in the context of IFNα-treated melanoma is of clinical importance, as it has been associated with significantly increased survival (5). Our patient, who developed autoimmune manifestations, aslo experienced long overall survival.

PEG-IFNα-2b and matured dendritic cells-based immunotherapy represents a promising therapeutic approach to treat metastatic melanoma. However, latent autoimmune diseases may be exacerbated by immunotherapy, and specific caution is required in patients with autoantibodies in the absence of clinical manifestations. We recommend close monitoring of autoantibodies in patients with melanoma treated with IFN and dendritic cells.

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