atitudes and beliefs regarding sun protection and exposure behaviors and skin cancer prevention among Puerto Rican adults.

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Accepted for Publication: October 4, 2013.


Author Contributions: Dr Coups had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Coups.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Coups.

Obtained funding: Tortolero-Luna.

Administrative, technical, or material support: Tortolero-Luna.

Conflict of Interests Disclosures: None reported.


Risk for Nevus Transformation and Melanoma Proliferation and Invasion During Natalizumab Treatment: Four Years of Dermoscopic Follow-up With Immunohistological Studies and Proliferation and Invasion Assays

Natalizumab is a monoclonal antibody targeting α4 integrin used to treat multiple sclerosis (MS). Seven cases of melanoma during natalizumab treatment have been reported since 2006.1-2 The objective of this study was to assess the effect of natalizumab on nevi transformation and tumor cell proliferation, invasion, and migration in preclinical models of melanoma.

Methods | We conducted an observational follow-up of all patients with MS treated with natalizumab in the University Hospital of Nice from January 1, 2008, through December 21, 2012. Institutional review board approval was waived. Oral informed consent was obtained for each patient. The clinical part of this study expanded a prior study3 of 44 patients from the same cohort. The evolution of nevi under treatment was assessed by clinical dermatologic examination and digital dermoscopy performed every 6 months. Nevi were examined and compared side by side with baseline photographs, and excision of suspect lesions was performed based on clinical and dermoscopic criteria. A combined in vitro approach was performed to analyze the effect of natalizumab on the proliferative, invasive, and transmigratory behavior of melanoma cells (detailed information is provided in the eMethods of the Supplement).

Results | We included 74 patients with MS and monitored a total of 775 pigmented lesions. A mean of 11 lesions (range, 3-74) was observed for each patient. In consideration of the risk factors of melanoma, we noted that 27 patients had fair skin. Twenty-nine patients remembered experiencing frequent sunburns in childhood. Four patients had more than 50 nevi. Two patients had a familial history of melanoma. Two patients had a personal history of melanoma and were already being followed up for an atypical nevoid syndrome. One of these patients had 3 melanomas removed (1 in 2006 [in situ] and 2 in 2008 [Breslow thicknesses, 0.33 and 0.36 mm]) before receiving natalizumab since 2009. The median duration of follow-up was 19 (range, 6-48) months. Twenty-three lesions (2.97%) showed modifications over time. Only 1.54% presented substantial dermoscopic changes (eFigure 1 in the Supplement). Seven melanocytic lesions were removed for histologic examination. Results for all 7 were benign. The 2 patients with a personal history of melanoma did not show any modification of their nevi.

Secreted matricellular SPARC (secreted protein acidic and rich in cysteine) and β3 integrin levels have been shown to be increased in melanoma and to promote melanoma invasion.4,5 We next analyzed whether natalizumab therapy induced changes in the expression of SPARC and β3 integrin. In the nevi removed from natalizumab-treated patients, melanocytic cells did not show a positive reaction with anti-SPARC antibody in contrast to that observed in the melanoma sample (Figure 1A). In addition, β3 integrin was virtually absent in nevi analyzed from the MS patients (Figure 1B).

We then evaluated the effect of natalizumab on the proliferative and invasive phenotypes of melanoma cells in vitro. Proliferation of A375 melanoma cells treated with natalizumab was similar to that of untreated cells (eFigure 2 in the Supplement). However, a dose-dependent reduction of tumor cell migration and invasion in response to natalizumab treatment was noted (Figure 2). Natalizumab also decreased the ability of melanoma cells to migrate across endothelial monolayers (eFigure 3 in the Supplement).

Discussion | Among the 74 patients with 775 monitored melanocytic skin lesions followed up for more than 4 years, sub-
Substantial dermoscopic changes were observed in only 1.54% of the cases. Results of histologic analysis revealed all the excised lesions to be benign, and no melanoma was diagnosed. After a mean duration of follow-up of 14 (range, 6-20) months of the same cohort with 44 patients included at that time and 248 nevi examined, substantial dermoscopic changes were observed in 4.8% of the cases. In an untreated population, substantial dermoscopic changes were observed in about 4% of common and atypical nevi after a median total follow-up of 11 (range, 3-21) months.

Unlike melanoma, the nevi removed during the follow-up of the patients treated with natalizumab did not show detectable levels of SPARC and β3 integrin, indicating that natalizumab therapy did not modulate expression of melanoma progression markers in nevi. Melanoma cell migration and invasion were significantly and proportionally reduced with increasing doses of natalizumab. Natalizumab also inhibited transendothelial migration across activated vascular cell adhesion molecule 1-expressing endothelial cells.

Collectively, these results further support that natalizumab therapy does not increase the risk for nevus transformation and that natalizumab exerts anti-invasive and antimigratory activities in vitro. Because these capabilities of...
malignant cells correlate with their metastatic potency, our findings provide evidence that natalizumab might have a protective effect on melanoma development and give reassuring data for its use in treatment of MS.

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Accepted for Publication: October 30, 2013.


Author Contributions: Drs Tartare-Deckert and Passeron had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed equally to this work.  
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Statistical analysis: Pharaon, Tichet.

Obtained funding: Tartare-Deckert.

Administrative, technical, or material support: Lebrun-Frénay, Tartare-Deckert, Passeron.

Study supervision: Lebrun-Frénay, Tartare-Deckert, Passeron.

Conflict of Interest Disclosures: Dr Lebrun-Frénay participated in meetings sponsored by and received honoraria for lectures, advisory board participation, and consultations from Allergan, Almirall, Biogen Idec, Bayer Schering, Genzyme, Merck Serono, Novartis, sanofi-aventis, and Teva. Dr Passeron participated in meetings sponsored by and received honoraria for lectures, advisory board participation, and consultations from Abbott, Almirall, Bioderma, Candela/Syneron, Beiersdorf, GSK, Jansen, L'Oreal, Léo-Pharma, Merck, Pierre Fabre, Pfizer, and Sinclair-Pharma. No other disclosures were reported.

Funding/Support: This study was supported by INSERM and the Fondation ARC.

Role of the Sponsors: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the C3M imaging core facility (Microscopy and Imaging platform Côte d’Azur [MICAD]) for immunofluorescent analysis. Emeline Castela, MD (Department of Dermatology, CHU Nice), Muriel Laffon, MD (Department of Neurology, CHU Nice), Philippe Bahadoran, MD, PhD (Department of Dermatology and Centre de Recherche Clinique, CHU Nice), Fanny Rocher, PharmD (Centre de Pharmacovigilance, CHU Nice), Mikaël Cohen, MD (Department of Neurology, CHU Nice), Patricia Abbe, BSc (INSERM, U1065, Team 11, C3M), Nathalie Cardot-Leccia, MD (Department of Pathology, CHU Nice), and Jean-Philippe Lacour, MD (Department of Dermatology, CHU Nice), provided medical and technical help. None received financial compensation for their services.


OBSERVATION

Cholesterol Embolization Syndrome With an Atypical Proximal Presentation Simulating Calciphylaxis

Cholesterol embolization syndrome (CES) is associated with endovascular procedures or anticoagulation, which disrupt atheromatous plaques within large arteries releasing cholesterol crystals. These crystals lodge in the vasculature of various organs, most commonly the skin. Cutaneous involvement classically presents in the distal lower extremities as livedo reticularis (49%), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%), purpura (9%), and splinter hemorrhages. We report a case of CES with proximal cutaneous lesions mimicking calciphylaxis.

Report of a Case | A woman in her 50s with an approximately 20-pack-year smoking history experienced a myocardial infarction, prompting anticoagulation therapy with heparin, cardiac catheterization, and stent placement at an outside hospital. Postoperatively, she initiated aspirin and clopidogrel treatment. Seven days after initiation, her lower back, buttocks, and thighs developed painful erythematous plaques, which progressed to nodules and ulcerations over days to weeks. A biopsy performed at the outside hospital suggested vasculitis. Prednisone treatment was initiated, and clopidogrel therapy was discontinued. As her ulcers continued to enlarge and her proximal arms developed mottling, she was referred to our clinic for evaluation.

At presentation, she had normal blood pressure and no gastrointestinal or neurologic complaints. On the buttocks, thighs, and right calf were firm, tender, erythematous nodules and ulcerations with overlying eschar (Figure 1). Livid ulceroid plaques were present on the lower back, buttocks, thighs, and proximal arms bilaterally. The distal extremities appeared normal. We considered CES, given the lividoid changes and history of endovascular intervention, while calciphylaxis was considered based on the appearance and location of the lesions. We also considered medium-vessel vasculitis.

A 6-mm punch biopsy specimen from an ulcer on the buttock demonstrated cholesterol clefts in the lumen of deep dermal arteries without evidence of calciphylaxis or vasculitis (Figure 2). Aside from leukocytosis (white blood cell count, 18 000/μL), findings of other blood tests were normal, including vasculitis assays such as antinuclear antibody and antineutrophil cytoplasmic antibody tests. Results of retinal evaluation by our ophthalmology colleagues were unremarkable.