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INNOVATION HIGHLIGHT

Total Body Photography and Sequential Digital Dermoscopy Imaging for Melanoma Surveillance in Patients Starting Natalizumab for Multiple Sclerosis

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Introduction:	Natalizumab is an integrin receptor antagonist that has been approved by the Food and Drug Administration to treat multiple sclerosis and Crohn's disease. The drug has been linked to an increased risk of melanoma. This brief report highlights an innovative clinical approach for monitoring the skin of patients prescribed natalizumab.
Methods:	We include 2 cases from our skin oncology clinic and a literature review on the incidence of melanoma in patients prescribed natalizumab between 2004 and 2019.
Results:	In addition to our 2 cases, we found 193 reports of patients with melanoma who were prescribed natalizumab. We propose an innovative and proactive approach using total body photography and sequential digital dermoscopy imaging before starting and while treating patients with natalizumab.
Discussion:	Given the mechanism of action of natalizumab, many of the melanomas diagnosed likely arose from preexisting melanocytic nevi. Using total body photography before starting this high-risk medication and then sequential digital dermoscopy imaging will increase a dermatologist's ability to recognize new and preexisting skin lesions that have evolved since the patient began taking natalizumab.
Conclusions:	Using the latest non-invasive technology to detect skin cancer supports systematic and objective monitoring of changing melanocytic growths in patients prescribed natalizumab, resulting in earlier detection of melanoma and greater cure rates.
Keywords:	total body photography, dermoscopy, melanoma, multiple sclerosis, natalizumab, Crohn's disease

Natalizumab (Tysabri) is a recombinant, humanized monoclonal antibody that binds to $\alpha 4 \beta 1$ -integrin and blocks its interaction with vascular cell adhesion molecule-1. As a result, leukocyte migration into brain tissue is inhibited, reducing inflammation and preventing the formation of lesions.¹ Natalizumab is approved by the Food and Drug Administration (FDA) to treat multiple sclerosis (MS) and Crohn's disease. Typically, this drug is given via a 1-hour infusion every 4 weeks.² On average, patients receive natalizumab

treatments over 30 infusions, or approximately 2.5 years.³

Natalizumab comes with a black box warning highlighting the increased risk of progressive multifocal leukoencephalopathy, a viral infection of the brain that can lead to death.² Yet, the FDA prescribing information does not mention that numerous reports correlated natalizumab and the development of melanoma, a potentially deadly skin cancer if not caught early.^{4,5,6} In one study from Italy, patients receiving natalizumab for MS were 3 times more likely to develop melanoma than the general population.⁷ It is still unclear how natalizumab promotes melanoma development. A recent study by Carbone et al did not find a direct link between

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natalizumab treatment and the development of cutaneous melanoma.⁸ Rather, natalizumab may indirectly favor melanoma progression by impairing the function of natural killer cells, therefore modifying the tumor microenvironment toward immune suppression and proangiogenesis.³

This brief report highlights an innovative clinical approach for monitoring the skin in patients prescribed natalizumab.

METHODS

Maine Medical Partners Dermatology has a dedicated skin oncology clinic with cutting-edge technology (not widely available) to support their care of patients prescribed high-risk medications or who have a history of melanoma or multiple non-melanoma skin cancers. One type of this technology is total body photography (TBP). High-quality, whole-body images of the patient's pigmented skin lesions are taken via FotoFinder, a computerized system that maps moles. This technology also allows for high-resolution digital dermoscopy with up to 140× magnification.⁹ Dermoscopy supports in vivo evaluation of colors and structures of the epidermis and parts of the dermis not visible to the naked eye.¹⁰ Sequential digital dermoscopy imaging (SDDI) offers a time-lapse comparative of pigmented skin lesions at different time intervals, supporting detection of changes as subtle as 1/10 millimeter.¹¹ Another type of cutting-edge technology is reflectance confocal microscopy (RCM). This non-invasive technique supports analysis of growths at the cellular level in vivo. RCM and TBP have been shown to aid in melanoma detection.

We include 2 case reports from our skin oncology clinic. Formal written consent was obtained. We also reviewed the literature for the incidence of melanoma in patients prescribed natalizumab. Information on natalizumab-associated melanomas was identified by examining peer-reviewed literature in PubMed from 2004 to 2019 using the keywords "natalizumab" and "melanoma." Articles reviewed were limited to the English language.

Based on our findings of numerous reports describing natalizumab-associated melanomas, we partnered with the Center for Comprehensive MS Care at Maine Medical Partners Neurology to develop an innovative management strategy for monitoring skin cancer. This center cares for

approximately 1250 patients with MS and 280 patients with other demyelinating diseases. In 2020, approximately 76 patients at the clinic were treated with natalizumab.

RESULTS

Case reports

Case 1: A 35-year-old female with no prior history of skin cancer was given natalizumab for MS for approximately 3 years before she presented with an enlarging pigmented growth on the lateral aspect of her right thigh (Figure 1A). The growth had been present since her childhood and became darker and larger shortly after she started treatment with natalizumab. Dermoscopy revealed a disorganized pattern within a melanocytic growth. Also present were shiny white structures, a blue-gray veil, and dotted vessels (Figure 1B). Due to concern for melanoma, she underwent a saucerization skin biopsy for depth and breadth under local anesthesia. The pathology report showed a superficial spreading malignant melanoma, stage 1b (0.8 mm, no ulceration), with peripheral and deep margins free of involvement. Her treatment with natalizumab was stopped and, per current guideline recommendations, she was referred to surgical oncology for a wide local excision and sentinel lymph node biopsy.¹² Negative margins were achieved and the results of the sentinel lymph node biopsy were negative. She is currently taking dimethyl fumarate (Tecfidera) for MS. To date, since stopping natalizumab, the patient has not presented with new skin lesions concerning for melanoma.

Case 2: A 37-year-old female with no prior history of skin cancer was given natalizumab for MS for 6 months before she developed several new melanocytic growths on her torso and bilateral lower extremities. Natalizumab was discontinued after 6 doses of therapy. Four months later, a melanoma was diagnosed on her back. Similar to Case 1, her treatment for MS was initially switched to Tecfidera. The patient has since undergone several changes in therapy and her disease continues to progress. To date, the patient has had no reports of new or changing nevi concerning for skin cancer.

Literature review (Table 1)

In addition to 2 cases from our skin oncology clinic, we found 193 reports of melanoma associated with natalizumab.^{4,5,6}



Figure 1. Melanocytic Growth in Patient Prescribed Natalizumab. (A) Clinical photo and (B) polarized dermoscopic image of 1.6 cm melanocytic growth on lateral aspect of right thigh

Sabol et al detailed an individual case report and included findings from both the FDA's Adverse Event Reporting System and their own literature search. The impetus behind their investigation stemmed from the development of a deadly urethral melanoma in a 43-year-old female with MS taking natalizumab for more than 2 years. Before April 1, 2014, there were 137 cases of natalizumab-associated melanomas reported to the Adverse Event Reporting System. An additional 45 cases were reported between April 1, 2014 and June 30, 2016. Of the cases reported up to April 2014, most were females being treated with natalizumab for MS. The median age at melanoma diagnosis was 45. Diagnosis was typically made within 2 years of natalizumab treatment. Most cases of natalizumab-associated melanoma were treated successfully with surgery. Nine patients (6.6%) died from melanoma complications.

In the literature, Sabol et al found 7 additional cases of patients with MS who were taking natalizumab and developed melanoma, confirmed by biopsy. All but 1 case involved a female. The median age was 41 years, and the melanoma diagnosis occurred after a median of 12 doses of natalizumab. These 7 published cases include those reported by Vavricka et al and Mullen et al, which were part of our literature review.

Vavricka et al reported 1 case of a 41-year-old female with a history of atypical nevi who was taking natalizumab for MS for approximately 15 months. At this time, she developed a rapidly growing nevus on her upper arm that was later diagnosed as melanoma in situ and was excised successfully.

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Mullen et al wrote a letter to the editor of the New England Journal of Medicine highlighting 2 cases of natalizumab-associated melanoma in women in their mid-forties with a diagnosis of MS. One patient was a 46-year-old female who noticed a rapidly changing nevus on her shoulder shortly after taking her first dose of natalizumab. The biopsy revealed a thick, non-ulcerated melanoma with metastases to the lymph nodes. The second patient was a 45-year-old female who developed ocular melanoma from a longstanding ocular nevus after taking several doses of natalizumab.

Innovative proposal

We propose an innovative and proactive approach using TBP and SDDI before starting and while treating patients with natalizumab.

1. Before starting natalizumab, the patient should be seen by a dermatologist for a full-body skin examination with dermoscopy.
 - a. Lesions that are worrisome for melanoma should be either biopsied or further evaluated using RCM.
2. The patient should undergo baseline TBP with digital dermoscopic imaging.
3. The patient should be evaluated against baseline images every 4 to 6 months. New or changing growths should be biopsied.

We suspect our patients (and many of the reported cases) had tenuous melanocytic growths before starting natalizumab treatment, and the medication enabled the progression by adversely impacting

Table 1. Literature Review of Case Reports of Natalizumab-Associated Melanomas

Author	Age, y	Sex	# of doses at melanoma diagnosis	Clinical features	Other information
Sabol et al (2017)	43	F	Unknown (estimated 2.2 y of treatment)	Polyp in distal urethra positive for melanoma.	Patient died from widely metastatic malignant urethral melanoma.
	38	M	5	--	Patient died from melanoma.
	39	F	5	After 10 months, ulcerated and ablated. 1.6 mm thickness and Clark level IV. No metastasis to lymph nodes.	Therapy stopped after 16 doses.
	38	F	77	Malignant melanoma. Clark level III and Breslow index 0.5 mm.	No evidence of metastasis.
	48	F	35	5 months after last dose, noticed enlarging mole on right shin. Lesion was flat with a dark center.	No evidence of metastasis or recurrence.
Sabol et al (2017), Vavricka et al (2011)	41	F	12	Superficial spreading melanoma from a dysplastic nevus on upper arm.	Had many atypical moles for years. Melanoma occurrence close to therapy start.
Sabol et al (2017), Mullen et al (2008)	46	F	1	Mole on shoulder for a long time before melanoma. Had metastatic spread to regional lymph nodes.	After discontinuing therapy, patient developed widely metastatic melanoma.
	45	F	Several	Ocular melanoma. Long history of mole in posterior eye. Mole was unchanged for 6 years before therapy.	Family history of melanoma.

DISCUSSION

The majority of melanomas diagnosed in patients taking natalizumab develop within approximately 2 years of beginning therapy, as was shown with Case 2.⁴ When melanoma is caught early, cure rates are nearly 100%.¹³ For patients prescribed natalizumab,

current recommendations include a full-body skin examination conducted by a dermatologist every 6 months after starting treatment.⁴ However, given the mechanism of action of natalizumab, many of the melanomas diagnosed likely arose from preexisting melanocytic nevi, as seen in Case 1.

immune surveillance. Thus, instead of waiting until a patient has already started treatment with natalizumab, we propose an innovative and proactive approach using TBP and SDDI. Much literature supports our assertion that TBP and SDDI will increase a dermatologist's ability to recognize new and preexisting skin lesions that have evolved since a patient began taking natalizumab.^{14,15,16,17} In patients over age 50, 30% of new growths identified with TBP are melanoma.⁶ Furthermore, using TBP and SDDI, one study monitored 11,396 lesions on 629 patients at high risk for developing melanoma.¹⁴ A total of 98 melanomas (8.5% of excised lesions) were diagnosed in 78 patients (12.6%). These lesions were identified at an early stage; 53 were superficial (in situ), 45 had a Breslow index (depth of tumor invasion) of < 1.0 mm (median 0.5 mm), and all were without ulceration (presence of ulceration portends a higher risk for metastasis).¹⁴

CONCLUSIONS

Patients prescribed natalizumab have an increased risk for developing melanoma from new and preexisting skin lesions. Proactive TBP and SDDI using our innovative approach supports improved monitoring of melanocytic skin growths in a systematic, objective way that may detect melanoma at earlier stages in high-risk patients. For optimal outcomes, a partnership is essential between the neurologist who prescribes natalizumab and the dermatologist who monitors the skin.

Lastly, this brief report is timely. In October 2020, the Journal of the American Academy of Dermatology issued a statement encouraging dermatologists to use TBP with SDDI and RCM to aid in detecting skin melanoma.¹⁸ The skin oncology clinic at Maine Medical Partners offers all these cutting-edge technologies.

Conflict of Interest: None

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