REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
10/26/2017	Poster	10/26/2017-10/29/2017

4. TITLE AND SUBTITLE
Melanoma or Pseudo-melanoma? Change in a pigmented lesion after application of topical 5-Fluorouracil.

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER
17388

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
59th Clinical Research Division
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JBSA-Lackland, TX 78236-9908
210-292-7141

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release. Distribution is unlimited.

13. SUPPLEMENTARY NOTES
American Society of Dermatopathology, Baltimore, MD, 26-29 October 2017.

14. ABSTRACT
5-fluorouracil (5-FU) is a topical chemotherapeutic agent used to treat actinic keratosis and superficial basal cell carcinomas. Common side effects include photosensitivity, erythema, ulceration and rarely hyperpigmentation. We present the case of a 56 year old, skin type 1 female that demonstrated a morphologic change in a pigmented lesion following topical field therapy with 5-FU for actinic damage on the trunk. After four weeks of twice daily application, a previously benign appearing pigmented lesion displayed a change in clinical morphology that included border irregularity, pigmentary change, scaling and erythema. A biopsy of the lesion demonstrated a poorly circumscribed and asymmetric compound proliferation of melanocytes with irregularly distributed junctional nests, solitary units and prominent pagetoid scatter. The epidermis showed large clusters of necrotic keratinocytes, dense pigment and sub-epidermal clefting. Fluorescent in-situ hybridization (FISH) was performed on additional sections and did not demonstrate chromosomal aberrations. Review of the literature demonstrated few reports of eruptive lentigo-maligna and atypical nevi occurring in patients undergoing therapy with oral 5-FU suggesting immunosuppression induced melanocytic proliferations or malign

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE	UU		Clarice Longoria
					19b. TELEPHONE NUMBER *(Include area code)* 210-292-7141

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Melanoma or Pseudo-melanoma?
Change in a pigmented lesion after application of topical 5-Fluorouracil.

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Abstract

5-fluorouracil (5-FU) is a topical chemotherapeutic agent used to treat actinic keratosis and superficial basal cell carcinomas. Common side effects include photosensitivity, erythema, ulceration and rarely hyperpigmentation. We present the case of a 56 year old, skin type 1 female that demonstrated a morphologic change in a pigmented lesion following topical field therapy with 5-FU for actinic damage on the trunk. After four weeks of twice daily application, a previously benign appearing pigmented lesion displayed a change in clinical morphology that included border irregularity, pigmentary change, scaling and erythema. A biopsy of the lesion demonstrated a poorly circumscribed and asymmetric compound proliferation of melanocytes with irregularly distributed junctional nests, solitary units and prominent pagetoid scatter. The epidermis showed large clusters of necrotic keratinocytes, dense pigment and sub-epidermal clefting. Fluorescent in-situ hybridization (FISH) was performed on additional sections and did not demonstrate chromosomal aberrations. Review of the literature demonstrated few reports of eruptive lentigo-maligna and atypical nevi occurring in patients undergoing therapy with oral 5-FU suggesting immunosuppression induced melanocytic proliferations or malignant transformation. No reports were found with topical 5-FU therapy.

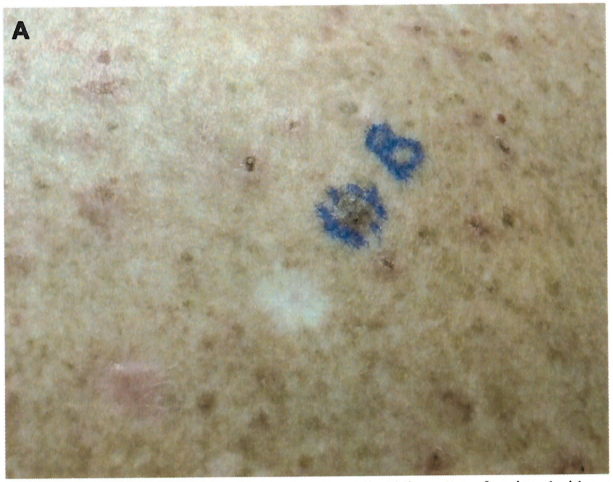
This case illustrates the difficulty when lesions are biopsied in a treatment field during or immediately following topical 5-FU therapy. The histopathologic features were consistent with melanoma; however, clinical suspicion for melanoma was not present until therapy was near completion. This raises a question as to whether this lesion was a melanoma that was not clinically apparent prior to therapy; was a benign lesion that transformed during therapy or is a pseudo-melanoma as the FISH studies showed no aberrations.

Case Report

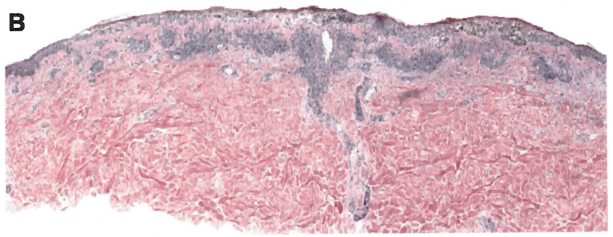
The patient is a 56 year old, skin type 1 female that demonstrated a morphologic change in a pigmented lesion following topical field therapy with 5-FU for actinic damage on the trunk. After four weeks of twice daily application, a previously benign appearing pigmented lesion displayed a change in clinical morphology that included border irregularity, pigmentary change, scaling and erythema.

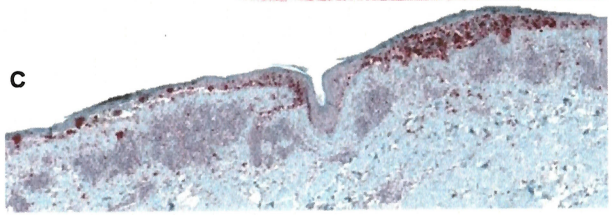
Histopathology

A biopsy of the lesion demonstrated a poorly circumscribed and asymmetric compound proliferation of melanocytes with irregularly distributed junctional nests, solitary units and prominent pagetoid scatter. The epidermis showed large clusters of necrotic keratinocytes, dense pigment and sub-epidermal clefting.

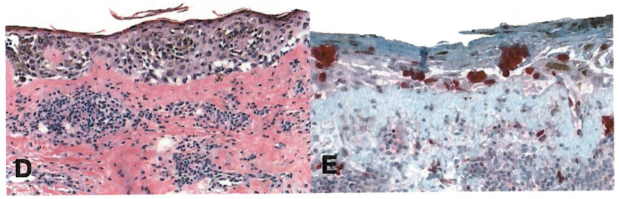


(A.) 7mm thin papule with irregular borders and multiple areas of variegated tan to dark brown color with slight induration and crusting.





(B) Upward scatter of pigmented melanocytes. Clefting artifact at the dermal epidermal junction. . (Hematoxylin and Eosin Stain, 100x magnification) (C) Mart-1 immunostain highlights the asymmetric melanocytic proliferation (100x magnification).



(D) H&E and (E) Mart-1 immunostain showing nests and solitary melanocytes with upward scatter (125x magnification).

Discussion

Eruptive melanocytic lesions with atypia in previously benign appearing melanocytic lesions have been described in patients undergoing systemic 5 FU therapy[1,2]. The pathogenesis is believed to be due to immunosuppression and subsequent melanocytic proliferation. The mechanism of action of 5 FU orally and topically are identical, which theoretically could induce the same immunosuppression, but only in the area of application as very little topical 5-FU is absorbed systemically.

Previous cases of oral 5 FU induced eruptive melanocytic lesions with atypia have described similar histopathologic features. These include large, atypical melanocytes arranged in nests and solitary units, epidermal atrophy and marked solar elastosis [1-3]. The differences between the current case and previous reports are the prominent pagetoid scatter and sub-epidermal clefting, which could be attributed to the direct application of the 5 FU. Pagetoid scatter of melanocytes has been described in traumatized nevi[4].

Flourescent in-situ hybridiation (FISH)can be a helpful adjuvant test in categorizing atypical melanocytic proliferations into benign or malignant based on aberrations (gains or losses) in loci on chromosomes 6 , 9 and11[5,6]. The reported sensitivity and specificity is 86% and 97%, respectively; however, melanomas can be negative for FISH aberrations [5]. This case was negative for the FISH alterations. FISH analysis of 5-FU induced melanocytic atypia has not been described. 5-FU alters DNA synthesis and repair, but its effects on melanocytes has not been evaluated. The significance of a negative FISH in this setting is unclear.

This case illustrates the difficulty when lesions are biopsied in a treatment field during or immediately following topical 5-FU therapy. The histopathologic features were consistent with melanoma; however, melanoma was not considered until therapy was near completion. This raises the question as to whether this lesion was a melanoma not clinically apparent prior to therapy; was a benign nevus or lentigo that transformed during therapy or a therapy induced pseudo-melanoma as the FISH studies showed no aberrations. The lesion was ultimately treated as a melanoma due to the architectural and cytologic features and the patient had a wide local excision to ensure complete removal.

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