Paradoxical Effect of Epinephrine on Lesion Redness and Vascularity

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Short Report

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Abstract

Introduction: Epinephrine is commonly used in combination with local anesthetic (lidocaine/epinephrine) due to its beneficial vasoconstrictive properties. Typically, pallor is appreciated after injection as a sign of effect; however, we observed that some cutaneous malignancies paradoxically revealed increased redness and vascularity after injection of lidocaine/epinephrine. In this study, we investigate this phenomenon among a series of biopsied lesions to identify characteristics of lesions associated with increased redness and/or vascularity.

Objectives: To determine characteristics of lesions which become redder or more vascular after injection with lidocaine/epinephrine prior to biopsy.

Methods: This cross-sectional study consisted of a convenience sample of lesions scheduled for biopsy. Lesions were photographed prior to and 7 minutes after injection of lidocaine/epinephrine as a part of standard care. Two readers blinded to study objectives and histopathological diagnosis assessed lesions for changes in redness and vascular features.

Results: Fifty-four lesions from 47 patients—61.7% male, mean age 64.8 years, age-range 24-91 were included. Thirty-six lesions were biopsy confirmed malignant, with 5 in-situ and 31 invasive malignancies; the remaining 18 lesions were benign. In comparison to non-malignant lesions, malignant lesions were associated with an increase in clinically appreciable vascular features after injection of lidocaine/epinephrine, X_2 (1) = 21.600, p<0.001. Further stratification into benign, in-situ, and invasive lesions strengthened the association, X_2 (1) = 23.272, p<0.001.

Conclusions: Combination lidocaine/epinephrine has been shown to paradoxically increase the visibility of vessels seen in cutaneous malignancies. This is consistent with prior literature suggesting aberrant adrenergic signaling in neoangiogenic vessels.

Introduction:

The diagnosis of skin cancer is dependent on the recognition of certain clinical and dermoscopic colors and structures.[1] Red structures commonly take the form of blood vessels or milky red areas and are often used as the differentiating diagnostic features for cutaneous malignancy. Recently, we observed dermoscopic red structures becoming more conspicuous in some cutaneous malignancies after injection of the combination of lidocaine/epinephrine prior to biopsy. This seemed paradoxical since epinephrine is added to local anesthetics for its vasoconstrictive properties, which prolong anesthetic effect and reduce bleeding in a visually appreciable form—blanching of the skin.[2] However, as neoangiogenic vessels in cutaneous malignancies have been shown to have aberrant adrenergic expression, perhaps we are observing a clinical manifestation of malignancy associated cellular change.[3,4]

Objectives:

In this cross-sectional study, we evaluate the change in redness and vascular features following local anesthetic injection in a variety of lesions scheduled for biopsy as part of the standard of care.

Methods:

A convenience sample of lesions biopsied on days a research fellow was available from September 2018 to January 2019 were included. All included lesions had either redness or vascularity on baseline dermoscopic exam (A.A.M.) and were imaged using non-contact dermoscopy prior to, and seven minutes[5] after injection with 1%-lidocaine/1:100,000-epinephrine. Before and after images were taken using fixed camera settings (ISO, white balance, aperture, shutter speed) on a Nikon D500 (Nikon, Tokyo, Japan) equipped with a Dermlite Foto II Pro dermoscopy lens (3Gen, San Juan Capistrano, California).

Two authors (N.G.M. and A.D.) blinded to the study objectives, histopathological diagnosis, and image attributes except for pre- and post-intervention status, reviewed images and reported any change in redness or vascular features (count, caliber, and prominence). In this analysis, invasive cancers included: squamous cell carcinomas (SCC), melanomas with an invasive component, and all basal cell carcinomas (BCC). In-situ cancers included: squamous cell carcinoma in-situ as well as melanoma in-situ. Benign lesions were defined as lesions not meeting inclusion criteria for either the invasive or in-situ categories. Descriptive statistics were used to describe patient and procedure characteristics. The associations between reported change with patient and lesion characteristics were evaluated with the Pearson's chi-square test. Analyses were performed using IBM SPSS v*27* (IBM Corp., Armonk, New York).

Results:

Fifty-four lesions from 47 patients—61.7% male, mean age 64.8 years, age-range 24-91—were included. Lesions were located on the trunk (57.4%), upper extremities (16.7%), head and neck (14.8%), and lower extremities (11.1%). Of the lesions, 36 were biopsy-confirmed malignant, with 5 in-situ and 31 invasive (Table 1). Our evaluation showed that 29 of the 54 (53.7%) had an increase in either vessel count, prominence, or caliber. When evaluating both redness and vascularity, 36 of 54 lesions (66.7%) had an increase in either. The remaining 18 of 54 lesions (33.3%) reported no change or a decrease in both redness and vascularity.

In comparison to non-invasive lesions, invasive cancers were significantly associated with an increase in dermoscopically appreciable vascular features, X_2 (1) = 21.600, p<0.001 (Table 1). When stratified into benign, in-situ, and invasive categories, the association further strengthened, X_2 (1) = 23.272, p<0.001. No significant associations were observed when exclusively evaluating change in redness among these groupings. However, analysis evaluating change in either redness or vascularity remained significant, suggesting that a lesion's vascularity, not its overall redness, may be the pertinent dermoscopic feature to consider.

Discussion:

This pilot study shows that skin cancers, particularly those with an invasive component, are paradoxically associated with increased vascular features after injection with lidocaine/epinephrine. There are multiple possible explanations for this phenomenon. Increased redness may be the result of dilation of aberrant vessels which have increased β_2-adrenergic receptor expression—whose activation by epinephrine antagonizes α_1-driven vasoconstriction.[3,4] This may not be unprecedented, as prior literature has correlated the presence of β_2 adrenergic receptors with melanoma's Breslow thickness.[6] Redness may also be the result of the selective constriction of venules in response to epinephrine while the aberrant vascular supply of invasive lesions fails to constrict, thus leading to vascular congestion. While this and the physical compression of draining vasculature from the injected fluid volume could lead to congestion and redness, no change in redness or vascularity were anecdotally noted by A.A.M. when lidocaine alone was injected in cases where the patient reported an epinephrine sensitivity (data not shown). A recent study supports these findings, as blanching was noted with lidocaine/epinephrine injection, but not in their lidocaine-only and saline controls.[2]

Our study was limited by a relatively small sample size, the inclusion of a restricted number of tumor types, and lack of systematic evaluation of the effect of epinephrine and lidocaine alone.

Our findings may represent one of the first reports of a clinical correlation to aberrant adrenergic expression seen in the neoangiogenic vessels associated with cutaneous malignancy. This finding may also provide a valuable dermoscopic clue in the diagnostic process. Future studies should evaluate its implications for management, as a physician may elect to do a deeper and/or wider biopsy on lesions with increased vascularity after being injected with lidocaine/epinephrine.

Declarations:

Competing Interests Statement: None to declare for all authors.

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Author Contribution Statement:

Z.H.N. and A.A.M. wrote the main manuscript text, conducted statistical analysis, prepared table 1 and figure 1.

A.R. conducted data collection, data aggregation and statistical analysis.

K.K. conducted data aggregation and statistical analysis.

N.G.M. and A.D. were blinded reviewers.

K.L. and C.N.D. conducted data collection.

S.W.D. conducted data aggregation, statistical analysis, and statistical review.

All authors reviewed the manuscript.

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Tables:

Table 1 Chi-squared Analysis Comparing Lesion Characteristics and Increased Redness, Vascularity, and Redness/Vascularity

Lesion Characteristic	Change in Redness		Change in Vascularity		Change in Redness and/or Vascularity	
	Pearson's Chi-Square (df)	p-value	Pearson's Chi-Square (df)	p-value	Pearson's Chi-Square (df)	p-value
Region (trunk, upper extremity, head and neck, lower extremity)	13.354 (3)	0.004	0.254 (3)	0.968	1.491 (3)	0.684
Type of Lesion (benign, in-situ, invasive)	1.206 (2)	0.547	23.272 (2)	<0.001	13.396 (2)	<0.001
Malignant vs. Non-malignant	0.711 (1)	0.399	21.600 (1)	<0.001	12.623 (1)	<0.001
Invasive vs. Non-invasive	1.196 (1)	0.274	20.737 (1)	<0.001	11.686 (1)	<0.001
Diagnosis (bcc, scc, melanoma, lplk, nevus, other)	4.203 (5)	0.521	21.988 (5)	<0.001	17.422 (5)	0.004

Figures

Figure 1

(Top) Example of Invasive Nodular BCC with increased vascularity and redness, (Middle) Example of Invasive Melanoma (0.6mm) with increased vascularity, (Bottom) Example of a Lichen planus-like keratosis with no increased redness or vascularity. Images were segmented for improved visualization during comparison