ORIGINAL ARTICLE

An automated evaluation system of dermoscopic images of longitudinal melanonychia: proposition of a discrimination index for detecting early nail apparatus melanoma

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ABSTRACT

The prognosis of nail apparatus melanoma is generally poor because of difficulty in early stage diagnosis. Most nail apparatus melanomas occur as longitudinal melanonychia, and criteria and algorithms for dermoscopy diagnosis of longitudinal melanonychia have recently been proposed. However, as with any clinical diagnosis, the diagnosis based on dermoscopy is to some extent subjective. Our goal is to develop an automated dermoscopic screening system for longitudinal melanonychia and to propose a novel objective and quantitative index for discriminating early nail apparatus melanoma from benign longitudinal melanonychia including melanocytic nevus. We propose an automatically calculated index representing degrees of color variegation in dermoscopic images of longitudinal melanonychia. Dermoscopy images of 6 cases of early stage nail apparatus melanoma and 25 cases of benign longitudinal melanonychia were analyzed with our screening system and a threshold of melanoma discrimination index was determined. This single melanoma discrimination index diagnosed early nail apparatus melanoma with 100% sensitivity and 92% specificity. The automatically calculated index proposed in the present study is valuable for managing longitudinal melanonychia. The results suggest that the degree of color variegation is essentially different between early nail apparatus melanoma and benign longitudinal melanonychia including melanocytic nevus of the nail apparatus.

INTRODUCTION

Nail apparatus melanoma is a rare entity, accounting for only 0.7% to 3.5% of all cutaneous melanomas in white populations [1], but is less rare in non-white populations; about 9% of cutaneous melanomas in the Japanese population [2] and is much more common in black populations. The ratio differs among races but the absolute incidence of nail apparatus melanoma may well be similar among different racial groups. Due to difficulty in early stage diagnosis, the prognosis of nail apparatus melanoma is generally poor.

Dermoscopy is a useful tool for the diagnosis of cutaneous melanomas because it introduces a new morphological dimension that is not visible to the naked eye. The same is also true for nail pigmentation. Based on previous studies by Johr et al. [3] and Kawabata et al. [4], Ronger et al. proposed dermoscopic criteria for the diagnosis of various categories seen as longitudinal melanonychia [5]. Their criteria for nail apparatus melanoma were as follows: longitudinal brown to black parallel lines with irregular coloration, spacing, or thickness, and disruption of parallelism with a brown background. In contrast, longitudinal melanonychia of melanocytic nevus exhibits regular parallel lines on a brown background. These findings by Ronger et al. [5] prompted Tosti [6] and Braun et al. [7] to propose algorithms for dermoscopic diagnosis of longitudinal melanonychia. These algorithms use differences in coloration and morphology as important clues. However, as with any other clinical diagnosis, diagnosis based on dermoscopy is to some extent subjective.

There have been many studies using digital image analysis for the diagnosis of melanomas on non-glabrous skin [8)-15)]. However, to our knowledge, there have been no such studies dealing with nail apparatus melanoma. This is probably partly because nail apparatus melanoma is rare and partly because, as mentioned above, predictive morphological features are significantly different from those in other cutaneous melanomas. Nakatochi et al. [16)] proposed an algorithm for automatic screening of nail apparatus melanoma based on morphological pattern recognition, which achieved a diagnostic accuracy of 80.0%. Color features were not taken into account in their study.

In this paper, we propose a novel objective index for discriminating early nail apparatus melanoma from benign longitudinal melanonychia including melanocytic nevus of the nail apparatus.

METHODS

Dermoscopy images of longitudinal melanonychia

A total of 31 longitudinal melanonychia lesions were retrospectively analyzed: 6 melanoma in situ lesions and 25 lesions of benign longitudinal melanonychia including melanocytic nevus. All patients were adult Japanese and had visited the dermatology outpatient clinic of Shinshu University Hospital from January 2005 through March 2008. All patients gave written informed consent for dermoscopic imaging and 6 patients with melanoma also gave consent for surgery. All melanoma in situ lesions were surgically removed and pathologically proven to be melanoma in situ. The 25

lesions of benign longitudinal melanonychia were not biopsied but none of the cases have since turned out to be melanoma over at least 5-year follow-up periods, which could confirm the benign nature of these lesions. Most lesions of benign longitudinal melanonychia were not grayish but brownish in color, suggesting most of them were melanocytic nevus, but some lesions of melanocytic activation could be included.

Most of the digital dermoscopic images of lesions were taken with a nonpolarized contact dermoscope (Derma 9500; Derma Medical Inc., Yokohama, Japan), combined with a digital camera (PowerShot A620 or PowerShot G11; Canon, Tokyo, Japan) with transparent jelly (K-Y jelly; Johnson & Johnson, South Africa) between the skin surface and dermoscope and were saved in JPEG format. Some images were taken with a nonpolarized contact dermoscope (Dermlite II Fluid; 3Gen, Dana Point, CA), combined with a digital HD video camera recorder (HDR-HC3; Sony Co., Tokyo, Japan) under the same conditions.

Pretreatment of images

For each digital dermoscopy image, only pixels belonging to the nail plates were retained, excluding pixels corresponding to nail folds, hyponychium and those with artifacts, such as air bubbles and halation with a commercially available graphics painting program (MS Paint; Microsoft Co. Ltd., Redmond, WA, USA). In this series, the Hutchinson's sign was detected in 4 of 6

melanomas but not detected in the benign group. Micro-Hutchinson's sign was not detected in both groups. The areas of Hutchinson's sign were excluded from the evaluation in this study. All of the remaining pixels were processed.

Melanoma discrimination index

Special emphasis was placed on RGB information of each pixel, with particular attention paid to color variations. As the three variables of R, G, and B are independent of each other, a three-dimensional color vector of $\mathbf{p}_i = (R_i, G_i, B_i)$ for the i-th pixel may be defined in a color space, i.e, Cartesian coordinate consisting of R, G, and B axes. Then, variation in colors were regarded as variations in direction of $\mathbf{p}_i$. To express the direction of $\mathbf{p}_i$ explicitly, we introduced the latitude, θ_i, and longitude, ϕ_i, which may be defined as follows:

$$\theta_i = \cos^{-1}\left(\frac{\sqrt{R_i^2 + G_i^2}}{\sqrt{R_i^2 + G_i^2 + B_i^2}}\right),$$

$$\phi_i = \cos^{-1}\left(\frac{R_i}{\sqrt{R_i^2 + G_i^2}}\right).$$

Here, θ_i and ϕ_i are measured from the RG plane and from the R axis in the RG plane, respectively (Figure 1). Throughout this paper, angles were measured in radian units. As the root mean square deviation (RMSD) of a set of (ϕ_i, θ_i) represents variation in the direction of $\mathbf{p}_i$, the RMSD value is used as a melanoma discrimination index (MI).

$$MI = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left\{\left(\theta_i - \overline{\theta}\right)^2 + \left(\phi_i - \overline{\phi}\right)^2\right\}},$$

where N is the total number of pixels used in the analysis and $\overline{\theta}$ ($\overline{\phi}$) is the averaged value of θ_i (ϕ_i). It is worth mentioning that plots in the (ϕ, θ) plane may also visualize malignancy of nail apparatus melanoma. All of the above procedures were performed with a mathematical calculation tool (MATLAB® 2009a; MathWorks Inc., Natick, MA, USA).

Statistical analysis

Statistical analyses were performed using the nonparametric procedure to verify the effectiveness of the melanoma discrimination index proposed in this paper. Statistical significance was set at 5%. Receiver operating characteristics (ROC) analysis was also performed.

RESULTS

Objective discrimination index

We investigated objective melanoma discrimination index using the set of 31 longitudinal melanonychia lesions, including 6 early lesions of nail apparatus melanoma. Figure 2 shows dermoscopy images (a, b) and plots of longitude (ϕ) and latitude (θ) (c, d) for a typical nail apparatus melanoma in situ (a, c) and a typical benign longitudinal melanonychia (b, d). The values of MI, i.e., RMSD, are indicated in panels (c) and (d) for each case. Comparison of Fig. 2c with Fig.

2d reveals that plots of (ϕ_i, θ_i) for the benign longitudinal melanonychia were distributed in a narrower region, while those for the early nail apparatus melanoma were more widely scattered in an asymmetric way. Note that the asterisks in Figs. 2c and 2d represent the direction where R, G, and B parameters contribute equally, i.e., $R_i : G_i : B_i = 1:1:1$. The biologic nature of these 2 lesions is expressed objectively by the proposed MI; MI=0.1625 for the melanoma in situ and MI=0.0511 for the benign longitudinal melanonychia. These observations suggest that variance in contribution of R, G, and B parameters is a significant indicator for early nail apparatus melanoma.

Figure 3 shows the distribution of MI for 6 lesions of nail apparatus melanoma in situ and 25 lesions of benign longitudinal melanonychia including melanocytic nevus of nail apparatus. The median, 25th percentile, and 75th percentile of MI for each group are indicated by bars in the Figure. Based on the nonparametric procedure, differences between the median of MI in the early nail apparatus melanoma group and that in the benign longitudinal melanonychia group were tested using the Mann-Whitney U-test. The null hypothesis was that the former is the same as the latter. A *P*-value of 0.0006, which was obtained using quasi-normal distribution, indicated that the null hypothesis could be safely rejected.

Diagnostic performance of the MI for nail apparatus melanoma in situ was evaluated using the ROC curve shown in Fig. 4. The single MI achieved 100% sensitivity and 92% specificity at the minimum balanced error rate where MI=0.0928 (see the dashed horizontal line in Fig. 3). The area

under the ROC curve (AUC) was 0.960, which exactly coincides with the probability of correct pairwise rankings in Wilcoxon statistics [17]. When AUC was tested, the null hypothesis was AUC=0.5, i.e., the MI is not a useful discriminator [17]. Using approximation to normal distribution of MI in the two groups, standard error was evaluated as 0.0528 [17], leading to z=8.85 ($p < 10^{-10}$) >1.96. Thus, the null hypothesis could be safely rejected. Figures 3 and 4 suggest that the proposed MI is a highly useful discriminator.

DISCUSSION

In the present study, we have proposed a melanoma discrimination index for diagnosing early nail apparatus melanoma. Its derivation procedures from digital dermoscopy images are quite simple, involving an objective and quantitative index measuring variation in contribution of R, G, and B parameters, i.e., the ratio of $R_i : G_i : B_i$. Note that the RMSD value of (ϕ_i, θ_i) is adopted as the discrimination index to avoid the influence of difference in individuals. The index can be automatically and promptly calculated with a conventional computer. The index achieved a high level of diagnostic accuracy, superior to dermoscopic diagnosis by experts [18].

The following should be mentioned. The sample size of the present training set was small. To increase statistical precision, e.g., keeping sensitivity of 90% and specificity of 90%, at least 35

samples in each group are needed [19].

Despite the small sample size, the present results are still instructive. Comparison of Figs. 2(c) with 2(d) indicates that a part of (ϕ_i, θ_i) for melanoma in situ tends to approach the origin along the line defined by $\theta = \phi$, although there are exceptions. This means that the dermoscopy images have some portions where red dominates over green and blue, i.e., $R >> G$ and $R >> B$. This feature suggests a decrease in the eumelanin : pheomelanin ratio in nail apparatus melanoma cells, just like uveal melanoma cells [20) 21).] Another explanation could be the rich vasculature in melanoma tissues.

Dermoscopic features are considerably different between advanced nail apparatus melanoma and nail apparatus melanocytic nevus [5).] However, the difference is often subtle between early nail apparatus melanoma and benign longitudinal melanonychia including nail apparatus nevus. The present results are quite instructive. A very simple index representing variegation in colors could well differentiate early nail apparatus melanoma from benign longitudinal melanonychia including melanocytic nevus of the nail apparatus. This suggests the following. The variation in contribution of R, G, and B parameters may reflect changes in pigment at the molecular level between melanomas and benign lesions. This may be due to excess production of pheomelanin and/or variegated production of eumelanin within lesions of early melanoma. Color variegation was reported to be one of the most important factors also in another automated screening systems for melanomas affecting

the non-glabrous skin [8].

Although the data are not shown here, highly advanced nail apparatus melanomas could show rather low discrimination index values. This may be because, in advanced melanoma, melanoma cell clones with higher proliferative potential predominate and cover most parts of the lesion, which may result in rather monotonous color of the lesion.

The performance of any automated melanoma diagnosis or screening system is usually assessed according to how precisely melanoma can be discriminated from benign pigmented lesions in a single assessment [3)-16) 22)23)]. When a threshold value is set so as to make the sensitivity nearly 100%, unnecessary excision of lesions may occur frequently, with patient harm as a consequence. To avoid such situations, a follow-up strategy should be added to any automated system. In the monitoring of longitudinal melanonychia, the objective index proposed here could provide useful information for management and avoid unnecessary excision of benign lesions. More importantly, missing of nail apparatus melanoma could be prevented with this digital monitoring. Further studies in larger numbers of cases are needed to verify its usefulness.

To encourage adoption of this diagnostic system, we will develop an original computer program that can be easily used by clinicians. We hope this evaluation method will be widely used and contribute to early detection of nail apparatus melanoma.

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FIGURE REGENDS

Figure 1. Definition of three-dimensional color vector of $\mathbf{p}_i = (R_i, G_i, B_i)$ for the i-th pixel and the corresponding latitude, θ_i, and longitude, ϕ_i.

Figure 2. Dermoscopy images of typical early nail apparatus melanoma (a) and benign longitudinal melanonychia (b). Panels (c) and (d) represent the distribution of longitude and latitude, (ϕ_i, θ_i), for the early nail apparatus melanoma and the benign longitudinal melanonychia, respectively. The dispersion of (ϕ_i, θ_i) is larger in early nail apparatus melanoma than in benign longitudinal melanonychia. Asterisks in panels (c) and (d) denote the direction of the grayscale axis. MI: melanoma discrimination index.

Figure 3. Distribution of the proposed melanoma discrimination index (MI) for the nail apparatus melanoma and benign longitudinal melanonychia groups. The median, 25th percentile, and 75th percentile of MI for each group are indicated by bars. The dashed horizontal line represents the threshold value at the minimum balanced error rate (see text). The difference in MI for the two groups was statistically significant, indicating the usefulness of MI for discriminating between the two entities.

Figure 4. Receiver operating characteristics (ROC) curve for the proposed discrimination index. The area under the curve (AUC) of 0.960 revealed that the index is a useful discriminator between early nail apparatus melanoma and benign longitudinal melanonychia including melanocytic nevus of the nail apparatus.

Figure 1

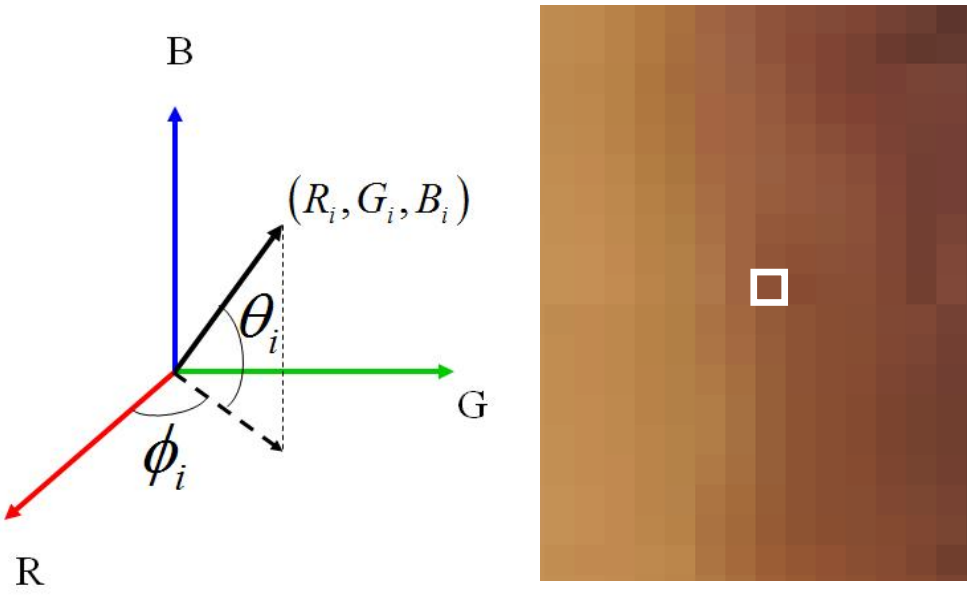

Figure 2

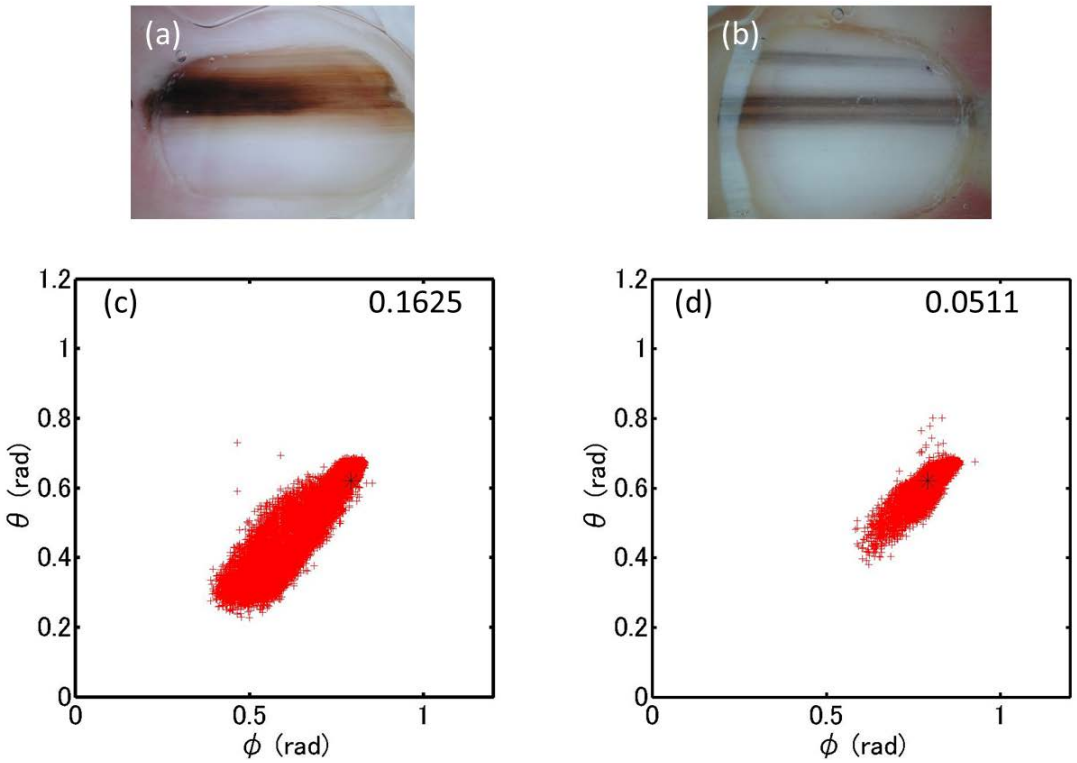

Figure 3

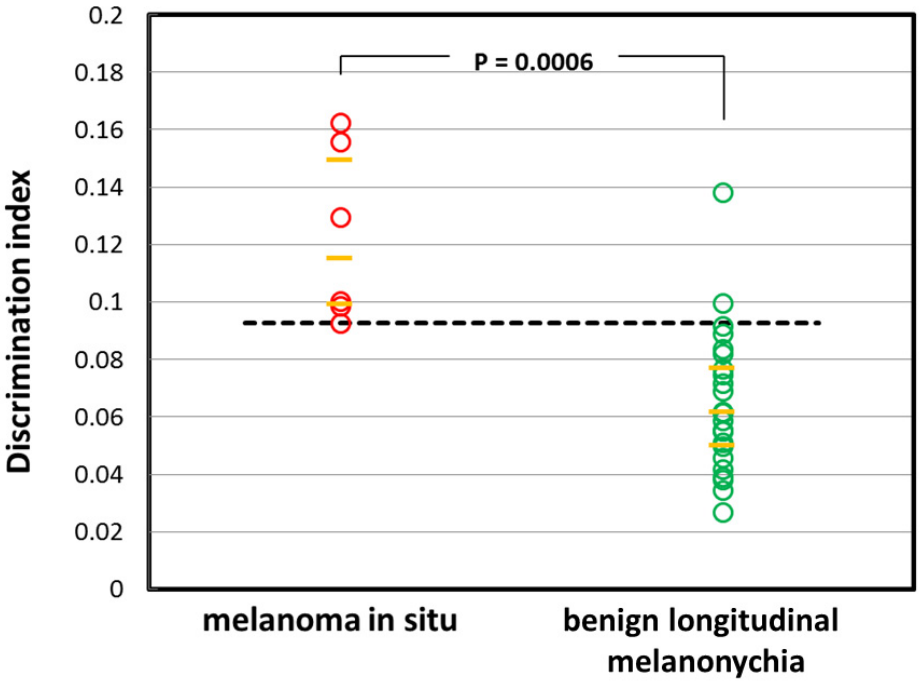

Figure 4