Diagnostic value of dermoscopy combined with reflectance confocal microscopy for clinically equivocal blue nevus

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Blue nevus (BN) is a benign, acquired pigmented lesion characterized by a bluish or dark-bluish pigmentation. Most lesions are benign and stable over time, sometimes developing into malignant blue nevus (MBN), a variant of malignant melanoma. The prognosis in MBN is at least as serious as in conventional melanoma.[1] Additionally, a differential diagnosis of BN including nodular melanoma, pigmented basal cell carcinoma, and cutaneous metastasis of melanoma may lead to excessive surgical excisions.

Non-invasive imaging techniques, such as dermoscopy and reflectance confocal microscopy (RCM), may be useful for diagnosis. The dermoscopic feature of BN is a global pattern characterized by a homogeneous bluish or steel-blue pigmentation. RCM may be a suitable tool for the diagnosis of BN since melanin is refractile at near-infrared wavelengths and melanocytic-derived cells are easily visualized. This study aimed to investigate the accuracy of dermoscopy, RCM, as well as the combination of dermoscopy and RCM in the diagnosis of BN, thereby confirming the hypothesis that the addition of RCM to dermoscopy might reduce the percentage of lesions for surgical biopsy. The study was approved by the Research Ethics Committee of China–Japan Friendship Hospital and conformed to the Declaration of Helsinki. After being completely notified of the procedures, written informed consent was obtained from all participants.

A total of 62 consecutive blue lesions with differential diagnoses including BN were collected from October 2017 to June 2019. Clinically, these lesions were suggested for surgical biopsies for an accurate diagnosis. Dermoscopic and RCM images were obtained before biopsy. Dermoscopic imaging was performed with a digital videodermoscope (FotoFinder, Bad Birnbach, Germany, Version from 2.0.27, Medicam 800HD). RCM images were acquired by a near-infrared reflectance confocal laser scanning microscope (VivaScope® 1500; Caliber ID, Henrietta, NY, USA), with only images considered relevant for diagnosis captured by RCM. Dermoscopic images were evaluated by two independent dermatologists to assess the diagnosis blindly to histological diagnosis. They passed both intermediate dermoscopic and RCM proficiency level tests. One week later, the same experts evaluated RCM images, followed by RCM + dermoscopy. All the images were provided in a different order and controversial images were evaluated by another expert.

Sensitivity, specificity, false positive rate (FPR), false-negative rate (FNR), positive predictive value (PPV), negative predictive value (NPV), Youden index of RCM, dermoscopy or RCM + dermoscopy were calculated. The internal consistency of histopathological diagnosis and imaging examination was expressed by Kappa values. The percentage of malignancy and suggested biopsies by different assessment methods were calculated. All data were analyzed using SPSS 21.0 software (IBMSPSS, Armonk, NY, USA). Fisher exact tests were performed to evaluate differences in proportions, with the area under the curves (AUCs) measured to evaluate diagnostic accuracy using Medcalc 19.0 software (MedCalc Software bvba, Mariakerke, Belgium) and the difference in AUCs compared by Delong test. A P value less than 0.05 was considered statistically significant.

The diagnosis according to the various assessment methods and histopathology is shown in Supplementary Table 1, http://links.lww.com/CM9/A276. The diagnostic accuracy of BN by AUCs was good for dermoscopy, RCM, and RCM + dermoscopy [Figure 1], with the difference being statistically significant. RCM + dermoscopy was the most accurate, followed by dermoscopy and RCM (dermoscopy *vs.* RCM, $P = 0.0018$; dermoscopy *vs.* RCM + dermoscopy, $P = 0.0075$; RCM *vs.* RCM + dermoscopy, $P < 0.001$). The sensitivity, specificity, FPR,

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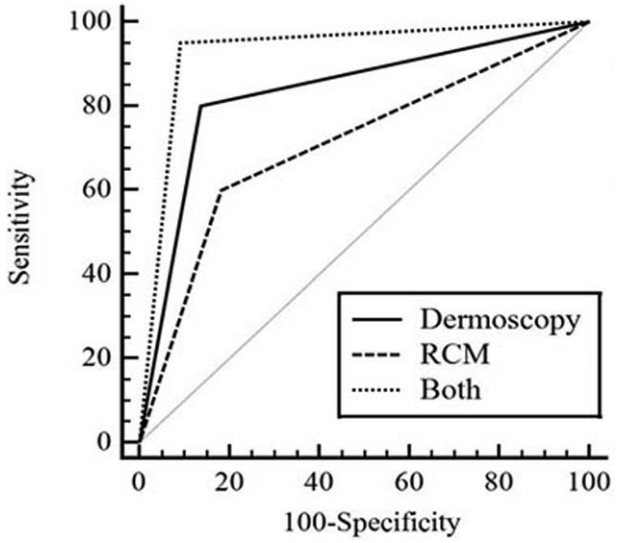

Figure 1: Diagnostic accuracy for blue nevus of dermoscopy, RCM, and both. RCM: Reflectance confocal microscopy.

FNR, PPV, NPV, Youden index of dermoscopy, RCM, and RCM + dermoscopy are listed in Supplementary Table 2, http://links.lww.com/CM9/A276. The combination of dermoscopy and RCM was consistent with the histopathological diagnosis, followed by dermoscopy alone, with poor agreement between RCM and histopathological diagnosis, with kappa values of 0.822, 0.631, and 0.372, respectively.

The evaluated percentage of malignancy was 22.5%, 2.5%, and 2.5% for dermoscopy, RCM, and RCM + dermoscopy, respectively ($P = 0.002$). The recommended biopsy accounted for 37.5%, 22.5%, 5.0% of all lesions by dermoscopy, RCM, and RCM + dermoscopy, respectively ($P = 0.001$). The percentages of malignant and benign lesions are listed in Supplementary Table 3, http://links.lww.com/CM9/A276, which also contains those lesions recommended for biopsy.

These results indicate that RCM had the lowest diagnostic accuracy for BN, possibly due to the limitation regarding the imaging depth of RCM and histopathological features of BN. RCM allows a detection depth to the papillary dermis, but a histological feature of BN is the pigmented spindle-shaped and dendritic melanocytes in the upper and middle dermis, so only a portion of lesions will be detected. This might also explain why some lesions were diagnosed as normal. Additionally, excessive fibrous tissue in the middle or upper reticular dermis leads to misdiagnosis as dermatofibroma. With minimum AUCs and kappa value in all methods, RCM alone might be insufficient for the diagnosis of BN.

Nearly a quarter of lesions were considered malignant and biopsies were suggested in one-third of lesions by dermoscopy. Previously, a malignancy and diagnostic biopsy should be considered if a blue color is detected within an image since it is present more frequently in malignant melanoma.[2] The positive predictive value of blue structures for any type of malignancy was reported to be 63.9%.[3] Subsequently, the blue hue within dermoscopy-blue areas was histopathologically diagnosed as melanocytic nevi, whereas a blue-whitish veil was highly indicative of malignant melanoma.[4,5] Inaccurate recognition of the two features might lead to unnecessary biopsies. RCM can improve the capacity to distinguish benign lesions from malignancy by providing further information regarding the tissue and cell morphology in a quasi-histological way.[6]

The percentage of lesions requiring biopsies was higher than those considered malignant by RCM. The main reason is that some lesions lacked specific changes, which may reduce the diagnostic confidence of investigators. Integration of RCM and dermoscopy combines advantages and overcomes the issues of the two imaging techniques, capturing the overall appearance, location of abnormal structures, and morphologic changes in individual cells. A combination of global and local characteristics leads to higher diagnostic accuracy and the lowest proportion of lesions recommended for histopathological examinations. Hence, if available, RCM is recommended when a diagnosis of BN is uncertain by dermoscopy.

There are some study limitations. First, the sample size was relatively small, as these lesions were clinically equivocal and not easy to collect. Even so, statistical analysis was unaffected by the sample size. Second, melanoma, dermafibroma, and basal cell carcinoma are other common differential diagnoses of BN, but the histopathological diagnosis of included lesions was confined to BN and intradermal nevus only. Thus, the suggested accuracy only refers to the differential diagnosis among BN and intradermal nevus. Third, MBN is one histological type of BN and exceedingly rare. The diagnosis of MBN relies on severely histologic atypical cytologic features, and there was no case in our study which proved to be MBN, so whether skin imaging technology can assist in the diagnosis of this entity remains uncertain. Further investigations involving a larger sample size and more cases of differential diagnosis are needed.

In conclusion, the assessment of the diagnostic accuracy of dermoscopy, RCM, and their combination for clinically equivocal BN indicates that RCM is not sufficient to assist with the diagnosis of this entity. A combination of dermoscopy and RCM has the highest diagnostic accuracy, so it is recommended for the diagnosis and dynamic monitoring of BN. Additionally, uncertain lesion by dermoscopy should be assessed by RCM to avoid unnecessary surgical excision.

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Conflicts of interest

None.

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