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· 临床研究 ·

反射式共聚焦显微镜对光化性唇炎的诊断研究

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【摘要】 目的 探究反射式共聚焦显微镜(reflectance confocal microscopy, RCM)在光化性唇炎诊断中的临床应用价值。**方法** 获得医院伦理委员会审批及患者知情同意, 回顾性分析2020年10月至2022年7月上海交通大学医学院附属第九人民医院就诊的17例诊断为光化性唇炎的患者, 用RCM扫描嘴唇白色过角化病损, 总结分析图像特征, 包括上皮增生/萎缩、过角化、炎症细胞浸润、血管扩张、日光弹性变、角质形成细胞异型性、细胞间间隙增宽、基底细胞层变性和色素沉着。并利用kappa一致性分析RCM和病理诊断的一致性。**结果** 光化性唇炎患者的上皮增生/萎缩、过角化、炎症细胞浸润、血管扩张和日光弹性变的组织病理特征在17例患者的RCM检查中出现的频率依次是76.5%、100%、100%、64.7%和70.6%; 以病理诊断为金标准, RCM诊断上述病变的正确率分别为82.4%、47.1%、94.1%、88.2%和76.5%。此外, 100%、88.2%、76.5%、88.2%的光化性唇炎患者分别显示角质形成细胞异型性、细胞间间隙增宽、基底细胞层变性、色素沉着的RCM特征。过角化和炎症细胞浸润特征的kappa值均为1, 血管扩张特征的kappa值为0.645。**结论** 反射式共聚焦显微镜对光化性唇炎的无创“活检”技术具有较好的临床诊断价值。

【关键词】 光化性唇炎; 反射式共聚焦显微镜; 过角化病损; 日光弹性变; 炎症浸润; 病理特征; 无创; 诊断技术

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Diagnostic study of actinic cheilitis by reflectance confocal microscopy ZHANG Muyang, WANG Haiyan, JIANG Weiwen. Department of Oral Mucosal Diseases, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, College of Stomatology, Shanghai Jiao Tong University, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Shanghai Key Laboratory of Stomatology, Shanghai Research Institute of Stomatology, Shanghai 200011, China

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【Abstract】 Objective To explore the clinical application value of reflectance confocal microscopy(RCM) in the diagnosis of actinic cheilitis(AC). **Methods** After approval by the hospital ethics committee and informed consent given by the patients, from October 2020 to July 2022, 17 patients who were diagnosed with actinic cheilitis in the Ninth People's Hospital affiliated with Shanghai Jiao Tong University School of Medicine were retrospectively analyzed. The white keratotic lesions of the lips were scanned with reflectance confocal microscopy, and the image characteristics were summarized and analyzed, including epithelial hyperplasia/atrophy, hyperkeratosis, inflammatory cell infiltration, blood vessel dilatation, solar elastosis, atypical keratinocytes, widening of intercellular spaces, degeneration of basal cell layer, and pigmentation. We used the sample compliance rate to measure the correlation between RCM parameters and histo-

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pathological diagnostic criteria for AC and kappa concordance analysis to calculate the concordance between RCM and pathological diagnosis. **Results** Under RCM, the sample correct rates for epithelial hyperplasia/atrophy, hyperkeratosis, inflammatory cell infiltration, vasodilation, and solar elastosis were 76.5%, 100%, 100%, 64.7%, and 70.6%, the sample accuracy compared with pathological diagnosis was 82.4%, 47.1%, 94.1%, 88.2% and 76.5%, respectively. We also observed that 100%, 88.2%, 76.5%, and 88.2% of AC patients showed RCM features of atypical keratinocytes, widening of intercellular spaces, degeneration of the basal cell layer, and pigmentation, respectively. The kappa value of hyperkeratosis and inflammatory cell infiltration was 1. The kappa value of blood vessel dilatation was 0.645. **Conclusion** Reflectance confocal microscopy is noninvasive and versatile and has clinical application value in the diagnosis of actinic cheilitis.

【Key words】 actinic cheilitis; reflectance confocal microscopy; keratotic lesions; solar elastosis; inflammatory infiltration; pathological features; non-invasive; diagnostic techniques

【Competing interests】 The authors declare no competing interests.

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光化性唇炎是一种唇部慢性炎症性疾病,是过度暴露于日光紫外线辐射的结果,通常影响下唇^[1]。经常暴露在阳光下的人最容易患上光化性唇炎^[2]。光化性唇炎临床表现为苍白、鳞屑、干燥、充血、慢性溃疡或糜烂^[3]。光化性唇炎的患病率为0.45%~2.4%^[4],在日晒等危险因素下会增加至43.2%。光化性唇炎向鳞状细胞癌(squamous-cell carcinoma, SCC)的恶性转化率为10%~30%^[5]。唇部95%的SCC发生在光化性唇炎的基础上^[6]。因此,光化性唇炎的早诊断早治疗具有重要意义。反射式共聚焦显微镜(reflectance confocal microscopy, RCM)是一种使用近红外激光的非侵入性工具^[7]。RCM可以高倍扫描皮肤和黏膜,并在细胞和亚细胞水平上拍摄图像,以很高的分辨率展示上皮和浅层结缔组织的形态,尤其是细胞及细胞间的形态特征,对血管、色素、胶原纤维、弹性纤维也能很好地展示^[8]。RCM优点是无创,并且实时、灵活,随时对疾病治疗过程和预后进行评估。RCM深度可达300~400 μm ,横向分辨率可达0.5~1.0 μm 。因此,RCM被称作是一种无创的“光学活检”技术,可以在显微镜水平上可视化组织结构,它与传统的组织病理学具有高度的一致性^[9-10]。光化性角化病是一种特征性病变,存在于长时间暴露紫外线辐射的皮肤区域^[11]。光化性角化病的临床特征是皮肤上粗糙、鳞状斑块或斑点,并伴有不同程度的过角化^[12]。光化性唇炎被认为是光化性角化病位于嘴唇的病损,并且和光化性角化病一样可以发展为鳞状细胞癌^[13-15]。近些年

RCM对光化性角化病的研究较为成熟。据国外研究人员报道,棘层的结构混乱和细胞多形性很可能是光化性角化病的RCM诊断标准^[16]。国内的学者研究发现,光化性角化病的RCM诊断标准包括表皮细胞排列紊乱和非典型角质形成细胞^[17]。然而,目前国内外对于发生于黏膜光化性唇炎的RCM研究仍然十分贫乏。因此,本研究拟观察和分析唇部黏膜光化性唇炎的RCM特征,为RCM在光化性唇炎的临床诊断提供参考。

1 材料和方法

1.1 一般资料

选取2020年10月至2022年7月于上海交通大学医学院附属第九人民医院就诊的光化性唇炎患者17例,其中男性患者5例(29%),女性患者12例(71%),平均年龄(67.4 ± 6.1)岁,平均病程(2 ± 1.6)年,平均室外工作史(37.5 ± 12.5)年,每天平均日晒时长(6.8 ± 2.5)h。

收集患者的临床资料,包括年龄、性别、病程、职业、日晒时间、RCM检查数据和病理切片资料。患者及家属签署了知情同意书。本研究已通过上海交通大学医学院附属第九人民医院伦理委员会审核(编号:SH9H-2023-T93-1)。

纳入标准:①下唇黏膜出现明确红色充血病损、白色病损(包括局部黏膜片状发白或者是白色条纹状)及弥散性色素沉着;②具有日晒史,临床诊断为光化性唇炎,并经RCM检查、组织病理学检

查诊断为光化性唇炎;③具有RCM数据;④知情同意这项回顾性研究的患者。排除标准:①临床诊断不是光化性唇炎的患者;②病理诊断不是光化性唇炎的患者。

1.2 方法

1.2.1 组织病理学检查 病理诊断由上海交通大学医学院附属第九人民医院口腔病理科有资质的病理医生出具。苏木精-伊红(H&E)染色、地衣红(Orcein)染色分别使用H&E试剂盒(M020,上海歌凡生物科技公司,中国)、Shikata地衣红染色试剂盒(M103,上海歌凡生物科技公司,中国),根据制造厂家说明书进行染色。

1.2.2 反射式共聚焦显微镜分析 RCM(美国Lucid公司,型号VivaScope® 3000,激光波长830 nm)具有大约30倍放大倍率的水浸物镜,其数值孔径为0.9 mm。RCM深度可达300~400 μm ,横向分辨率可达0.5~1.0 μm 。检查前对RCM进行校正,使零平面位于角质层最浅层。使用Vivastack模式并以2~3 μm 的间隔获取从角质层到结缔组织浅层的水平图像。

患者取坐位,选取下唇白色病损位点,将显微镜光源调至830 nm,将医用耦合剂挤入镜头中间,然后盖上塑料组织帽。用棉签蘸蒸馏水轻轻涂在病损处,使白色病损处湿润即可。扫描观察区域为

500 μm ×500 μm ,扫描范围为2 mm×2 mm(XY水平方向),扫描深度为350 μm 以内的上皮层及真皮浅层组织结构,由上而下进行扫描,采集各层次的RCM图像。

1.2.3 RCM观察特征 光化性唇炎的组织病理学诊断标准是上皮增生/萎缩、过角化、异常增生、炎症细胞浸润、血管扩张和日光弹性变,因此观察患者的RCM特征就包括上皮增生/萎缩、过角化、炎症细胞浸润、血管扩张和日光弹性变^[4]。由于异常增生的12个特征在RCM不能全部辨别,根据已有文献对RCM检测特征的描述,观察与异常增生及光化性唇炎相关的角质形成细胞异型性/上皮层不典型蜂窝状模式、细胞间间隙增宽、色素沉着和基底细胞层变性RCM特征^[18-19]。

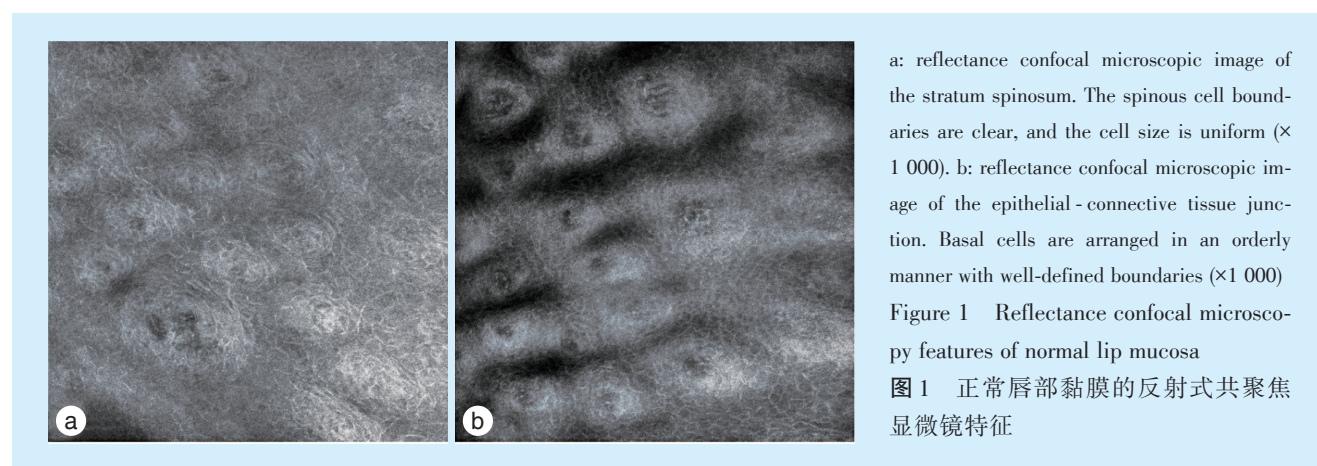
1.3 统计学分析

使用SPSS(23.0版)软件进行统计学分析。采用kappa检验、样本正确率来测试光化性唇炎的组织病理学特征与RCM参数之间的一致性。检验水准为 $\alpha = 0.05$ 。

2 结果

2.1 正常的口腔黏膜特征

RCM显示正常的口腔黏膜上皮细胞排列有序、细胞边界清晰、细胞大小均匀、基底膜清晰(图1)。



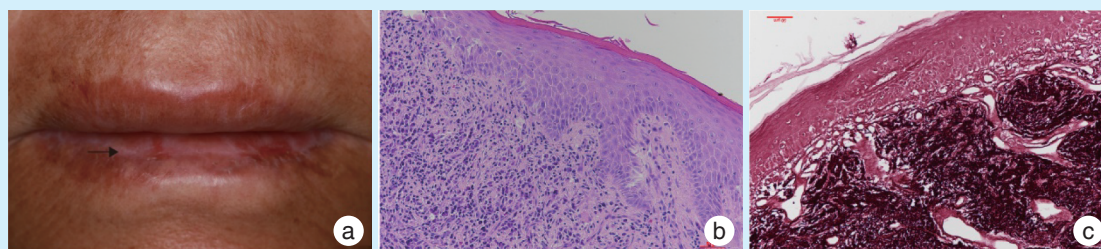
2.2 光化性唇炎患者的RCM特征

下唇白色病损处上皮平均厚度为(210.1 ± 56.7) μm 。光化性唇炎病理诊断标准包括上皮增生/萎缩、过角化、异常增生、炎症细胞浸润、血管扩张和日光弹性变。这些RCM特征在17例患者中出现的频率别为76.5%(上皮增生/萎缩)、100%(过角化)、100%(炎症细胞浸润)、64.7%(血管扩张)

和日光弹性变(70.6%)(图2、图3)。此外,有100%、88.2%、76.5%、88.2%的光化性唇炎患者显示角质形成细胞异型性、细胞间间隙增宽、基底细胞层变性、色素沉着的RCM特征。

2.3 RCM和组织病理学诊断的一致性分析

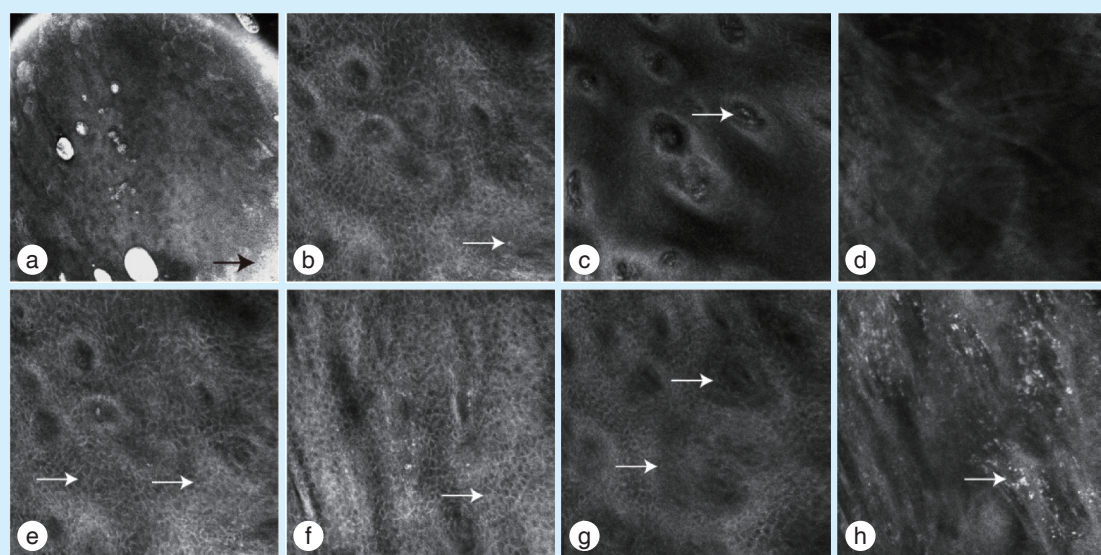
光化性唇炎的组织病理学诊断标准中,除了异常增生无法准确评估,上皮增生/萎缩、过角化、



a: actinic cheilitis reveals white hyperkeratosis plaque (black arrow), white patches, white striae, and hyperemia on the lower lip; b: H&E staining of actinic cheilitis (×200) reveals epithelial hyperplasia/atrophy, hyperkeratosis, dysplasia, inflammatory cell infiltration, blood vessel dilatation, and solar elastosis; keratinocyte atypia, widening of intercellular spaces, basal cell layer degeneration, and pigmentation; c: orcein staining for solar elastosis (×200): the connective tissue has a large number of elastic fibers that appear dark red

Figure 2 Clinical images and pathological changes of actinic cheilitis patients

图2 光化性唇炎患者的临床表现和病理变化



a: RCM image of hyperkeratosis (black arrow), a clumpy, highly refractive substance located in the stratum corneum, with amorphous cells (×1 000); b: RCM image of infiltration of inflammatory cells (white arrow), moderately refracted bright spots, scattered between cells (×1 000); c: RCM image of dilation of blood vessels (white arrow), connective tissue blood vessels flowing within the papilla (×1 000); d: RCM image of solar elastosis, there are white, thickened and widened elastic fibers in the superficial layer of connective tissue, the collagen fibers have undergone basophilic degeneration, and the collagen fibers are disorderly (×1 000); e: RCM image of atypical keratinocytes (white arrows), keratinocytes are abnormal in morphology and uneven in size (×1 000); f: RCM image of widening of the intercellular spaces (white arrow), the gap between cells is increased (×1 000); g: RCM image of degeneration of the basal cell layer (white arrows), the epithelial-connective tissue junction is poorly demarcated, and the basal cell boundary is absent and unclear (×1 000); h: RCM image of pigmentation (white arrow), highly refractive material is scattered in the epithelium and connective tissue (×1 000); RCM: reflectance confocal microscopy

Figure 3 Reflectance confocal microscopy features of actinic cheilitis patients

图3 光化性唇炎患者的反射式共聚焦显微镜特征

炎症细胞浸润、血管扩张和日光弹性变的样本正确率依次为82.4%、47.1%、94.1%、88.2%和76.5%。

17例光化性唇炎患者中,与RCM检测位点同一位点活检的配对组织病理诊断有11例,RCM非配对位点病理诊断的有6例。对具有病损RCM和配对病理诊断的11例光化性唇炎进行了kappa一致性

检验,上皮增生/萎缩的kappa值是0.389,过角化的kappa值是1,炎症细胞浸润的kappa值是1,血管扩张的kappa值是0.645,日光弹性变的kappa值是0。

3 讨论

本研究初步探讨了光化性唇炎的RCM诊断标

准,分别是上皮增生/萎缩、过角化、角质形成细胞异型性、细胞间间隙增宽、基底细胞层变性、炎症细胞浸润、血管扩张、日光弹性变和色素沉着。

光化性唇炎是一种癌前病变,临床上可表现为多种改变,比如充血、萎缩、白色斑块和色素沉着。正常口腔黏膜厚度为 $(173.5 \pm 20.5) \mu\text{m}$ ^[20]。目前,组织病理学仍然是诊断光化性唇炎的标准,必需进行活检来排除异常增生或者癌症^[21-22]。但是,由于嘴唇的解剖学和美容特征,患者希望避免活检,特别是多次活检^[19]。RCM可以对嘴唇进行无创实时的检查,因此,用RCM检查来代替活检具有重要的临床价值。本研究发现RCM检查和组织病理学分析具有较高的一致性,两种检查方式差异性较小。

根据文献报道,过角化、角质形成细胞异型性、上皮层不典型蜂窝状模式、炎症浸润、血管扩张和日光弹性变是光化性唇炎常见的RCM特征^[18,23]。本研究的数据和已有的发现是一致的,同时,笔者发现细胞间间隙增宽、色素沉着和基底细胞层变性也是光化性唇炎常见的RCM特征。有研究发现在上皮的棘层或基底层,可以在RCM下观察到明亮且形状不规则的角质形成细胞,其对应于色素沉着细胞^[24-25]。这些明亮的色素沉着很容易被RCM检测到^[8,26]。本研究17例光化性唇炎患者的白色过角化位点中,发现了15例患者存在色素沉着,说明色素沉着并不一定只存在于临床表现为黑色的下唇黏膜。

光化性角化病患者组织病理学和RCM检查之间过角化和炎症浸润的灵敏度分别为87.5%和68%^[27]。此外,有学者发现在组织病理学和RCM检查之间,光化性角化病患者血管扩张和日光弹性变这两个特征的灵敏度分别为64.8%和78%^[16]。本研究发现,以病理诊断为金标准,RCM诊断上皮增生/萎缩(82.4%)、炎症细胞浸润(94.1%)、血管扩张(88.2%)和日光弹性变(76.5%)的样本正确率都很高,表明这些RCM特征对于筛查可疑的光化性唇炎患者很有用。对于血管扩张,RCM和配对病理诊断有很好的一致性。对于炎症细胞浸润,RCM与配对病理诊断完全一致。因此,对于光化性唇炎患者,RCM检查可以用来辅助组织病理学检查。

世界卫生组织提出了上皮异常增生的12种组织病理学变化^[28-29]。而对于上皮基底细胞极性消失、上皮增生呈水滴状、上皮表层有丝分裂、有丝

分裂增加并伴有异常有丝分裂、细胞核浓染、细胞粘附减少,RCM评估较为困难。通过RCM只能看到异型性角质形成细胞存在形态不规则,而上皮异常增生无法评估,所以笔者没评估异常增生,只观察了角质形成细胞的形态异型性。对于上皮细胞分层不规则和紊乱、上皮基底细胞增生、细胞核质比增加、棘层单个或成簇细胞过早角化(角化不良)、细胞多形性、核仁大小增加,RCM是可以看出这些特征的。提示RCM可能在评估光化性唇炎的异常增生程度上较为欠缺。

综上所述,本研究证实了RCM在光化性唇炎诊断中潜在的临床应用价值和意义。RCM是一种灵活、无创的检查工具,可以筛查疑似光化性唇炎的患者,可以成为诊断光化性唇炎的辅助方法。

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