

共聚焦激光显微内镜在溃疡性结肠炎中的研究进展

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■背景资料

近年来,共聚焦激光显微内镜(confocal laser endomicroscopy, CLE)在溃疡性结肠炎(ulcerative colitis, UC)的发病机制、相关诊断、预后等方面做了多项研究,本文就以上方面作一综述。

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Application of confocal laser endomicroscopy in ulcerative colitis

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Abstract

The etiology of ulcerative colitis (UC) is not very clear. Most scholars believe that intestinal inflammation caused by immune system abnormalities plays an important role in the pathogenesis of UC. The clinical course of UC is characterized by episodes of exacerbation and remission alternately. Traditional electronic endoscopy with random biopsy plays an important role in the diagnosis, treatment and prognosis evaluation of UC. However, this method has some deficiencies, such as poor sensitivity, cumbersome procedures, bleeding caused by multiple biopsies and

other complications. The advent of high resolution confocal laser endomicroscopy (CLE) can allow real-time, noninvasive histopathological examination *in vivo*, to achieve the goal of "virtual biopsy". This paper reviews the application of CLE in UC.

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Key Words: Confocal laser endomicroscopy; Ulcerative colitis; Research progress

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摘要

溃疡性结肠炎(ulcerative colitis, UC)的病因尚不十分清楚,大多数学者认为肠道免疫系统异常所引起的炎症反应在其发病机制中起着重要作用,临床主要表现为发作期与缓解期交替的慢性病程经过,传统电子内镜及内镜引导下的随机活组织病理检查在疾病的诊断、治疗以及预后判断中发挥着重要作用,然而,上述方法存在灵敏度差、程序繁琐以及多处活检引起的出血等各种并发症的不足。随着技术的发展,高分辨率共聚焦激光显微内镜(confocal laser endomicroscopy, CLE)新设备在行常规内镜检查的同时,可以无创地实现实时在体组织病理学水平的检查,达到“虚拟活检”的目的,本文就CLE在UC中的研究应用作一综述。

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关键词: 共聚焦激光显微内镜; 溃疡性结肠炎; 研究进展

核心提示: 共聚焦激光显微内镜(confocal laser endomicroscopy, CLE)作为一种新兴设备, 无创的将内镜、组织病理学检查同步实施, 不仅简化检查步骤、提高诊断效率, 而且避免了内镜下随机活检带来的多种并发症, 在溃疡性结肠炎(ulcerative colitis)患者复杂的临床背景下, CLE作为一种新的显像模式有望得到很好的应用。

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0 引言

溃疡性结肠炎(ulcerative colitis, UC)是一种发病机制尚不十分明晰的慢性非特异性炎症性疾病, 病变主要累及结肠和直肠, 病变黏膜表现为连续性非阶段性分布的特点, 典型的临床表现主要有腹痛、腹泻、黏液脓血便等不适症状。内镜及内镜引导下的随机活组织病理学检查在UC患者的诊断、指导治疗、监测癌前病变及相关结直肠癌中起着不可替代的作用^[1-3]。共聚焦激光显微内镜(confocal laser endomicroscopy, CLE)作为一种新兴技术, 无创的将内镜、组织病理学检查同步实施, 不仅简化检查步骤、提高诊断效率^[4], 而且避免了随机活检带来的多种并发症。

CLE是基于机体局部(盐酸吡啶黄0.02%, 5-10 mL, 成像前30 s局部喷洒)或全身(荧光素钠10%, 5-10 mL, 静脉注射)应用荧光对比剂后, 应用低功率的激光照射组织而成像的一种新的内镜成像技术^[5,6]。他的工作原理是根据对所观察组织能获得放大1000倍的内镜图像, 联合荧光剂在不同组织中分布差异的特性, 由激光激发来观察组织结构的微观变化。UC的炎症病变限于黏膜及黏膜下层, 内镜及内镜下引导的活组织检查是判定疾病的标准, CLE的Z轴扫描范围从上皮细胞表层可达到固有层(0-250 μm)深度, 在检查病灶表面形态学结构的同时, 还能观测黏膜组织学的微观变化, 不但能达到即时“虚拟活检”的目的, 而且有利于靶向活检, 这使得CLE在UC患者中能得到很好的应用。目前可在临床中使用的CLE设备有两种类型, 一种是将微型化的共聚焦激光显

微镜头, 安装在传统电子内镜远端的整合式内镜(integrated confocal laser endomicroscopy, iCLE); 另一种则是将可移动性微探头通过传统电子内镜活检钳道, 可对靶组织进行检查的微探头式共聚焦激光显微内镜(probe-based confocal laser endomicroscopy, pCLE)^[7,8]。

1 CLE在UC患者发病机制中的研究

目前学者普遍认为炎症性肠病(inflammatory bowel disease, IBD)发病是多因素如环境、遗传及免疫等综合作用的结果, 其中细菌和免疫系统的相互作用是UC发病的关键作用机制^[9-12], Günther等^[13]做的一项研究指出, 肠黏膜细胞脱落作为一项潜在的作用机制, 可使肠道内细菌渗透到肠黏膜内, 多项涉及黏膜活检的细菌培养、PCR、免疫组织化学等技术已经用于检测黏膜内细菌的存在^[14,15], 然而活检样本的取出不仅破坏了黏膜的完整性及组织结构体系, 而且有碍于黏膜内细菌的准确定位, 介于CLE能获得实时活体黏膜层的内镜放大图像, Moussata等^[16]首先用CLE在UC患者的肠黏膜内细菌方面做了研究, 结果显示以荧光原位杂交技术作为判断的金标准, 静脉应用荧光素后CLE识别出黏膜内细菌的敏感性为89%、特异性为100%, 回顾性研究结果表明UC患者肠道黏膜内细菌较对照组显著增高, 这个结果同时被其指导的前瞻性研究所证实, 该研究同时指出UC患者结肠和回肠末端黏膜内的细菌和对照组相比明显增多。在2013年Neumann等^[17]做的一项研究中, 发现局部应用吡啶黄后, CLE也能观察到黏膜内细菌的存在。

在UC的发病机制中肠腔内的抗原、毒素、微生物渗透到肠壁是人们研究的反复主题^[18], 在炎症性肠道肠黏膜细胞脱落可使肠屏障功能受损, 一项试验为了证明CLE是否能够检测到黏膜细胞间隙及屏障功能障碍, 研究结果显示在炎症性肠道黏膜细胞脱落后造成的不完全封闭, 可使肠壁和肠腔间的物质相互流动, 在静脉应用荧光素后, CLE图像显示荧光素通过上皮细胞空隙渗漏到肠腔, 这是黏膜屏障功能障碍的生物学标志^[19], 在上皮细胞脱落部位非肠道正常微生物进入到肠壁可激活黏膜的免疫系统, 最终导致肠道慢性炎症^[20]。

2 CLE在UC相关诊断中的应用

目前认为UC和克罗恩病(Crohn's disease, CD)

■ 研发前沿

CLE使一些疾病的内镜诊断和病理组织学诊断有效地结合起来, 可以定位诊断、指导靶向活检, 并在将来有望取代耗时费力的传统组织病理切片技术。

■ 相关报道

CLE作为一种新型成像技术, 在Barrett's食管、胃上皮化生、乳糜泻、结肠腺瘤及结肠癌等多种胃肠道疾病中得到应用, 也已涉及对于胆管和肝等疾病的检查及检测。

■ 创新要点

近年来CLE在胃肠道癌前病变筛查及相关鉴别诊断等方面的文献报道较多,然而在UC疾病研究中的综合阐述尚缺乏,为方便大家能更全面及有针对性的学习相关知识,本文就CLE在UC方面的应用进展作一综述。

属于IBD的不同亚类^[21],对于IBD的治疗UC和CD的鉴别诊断是至关重要的,准确的诊断能够提供特定的治疗策略、预后评估以及可能的手术方式选择^[22-24]。CLE允许在内镜检查时体内表征体系结构和细胞细节,Tontini等^[25]第一次评估CLE鉴别UC和CD的有效性,该研究组依据CLE内镜成像所见提出了IDEA评分系统,内镜图像表现为和UC相关的异常结构包括:严重及弥漫的扭曲结构、不规则的肠道表面、隐窝减少,出现以上所见则每项加3分,而间断的畸形隐窝、局灶隐窝炎、不连续的炎症等和CD相关病变的缺失则每项加1分,评分范围为0-12分,<6分诊断为CD,≥6分为UC,用IDEA评分体系鉴别UC和CD的总体准确度93.7%。

慢性UC患者的腺瘤样肿块(adenoma-like mass, ALM)大多采用内镜下治疗,而不典型增生样变(dysplasia-associated lesion mass, DALM)被认为和高级别的上皮内瘤变和结直肠癌有关,多是采取结直肠手术切除方式^[26],正确治疗方式的选择需要对上述疾病进行准确的鉴别。Kiesslich等^[27]用CLE对36例ALM或DALM的患者进行在体鉴别诊断,分别在病变处及4处毗邻的黏膜部位进行显微成像,运用修改的美因兹标准,CLE在体诊断ALM及DALM的结果,和靶向活检的组织病理学的结果进行比较,研究显示诊断一致性的系数Kappa值为0.91,准确性为97%,在95%的可信区间86%-99%内。研究者^[28]得出运用CLE可以在体准确鉴别ALM及DALM结论,同时认为可安全的帮助患者选择合适的治疗方式。

UC患者长期反复发作的炎症反应,发展为结肠炎相关结直肠癌的危险明显增加^[29],为了降低患者患结直肠癌的风险及改善预后,及时发现上皮内瘤变等癌前病变并早期治疗是有效途径,AGA指南推荐诊断为UC病史达8年以上的患者,需要定期对全肠道进行活组织病理学检查^[30],尽管如此,仍有很多平坦、小病灶的遗漏^[5,29,31],而且广泛的活组织取样会带来出血等各种并发症的发生。CLE具有在体组织病理学观察的能力,在常规肠镜检查的同时可实现靶向活检,可减低样本取样量,提高病变检出率,减少漏诊的发生^[32,33]。有研究^[4,34-36]资料显示,染色内镜联合CLE在检出上皮内瘤变时,阳性率比传统肠镜检查高4.75倍,活检样本量减少50%,其敏感性和特异性分别为94.7%、98.3%,研究者认为CLE不仅增加了内镜检出上皮内瘤

变的阳性率,而且可显著减少组织活检需要的样本量。后来多项研究也证实了上述研究结论。

3 CLE在UC预后判断中的价值

CLE可检测出小肠细胞脱落造成的肠细胞间隙,Kiesslich等^[19]首先发现增加的小肠上皮细胞间隙密度使处于IBD临床缓解期患者复发的危险增加,另一项试验在于研究小肠上皮细胞间隙密度和UC患者的住院及手术率是否有关,入组20例UC患者,随访中位时间为14 mo,结果显示间隙密度高的UC患者住院及手术的风险更高,间隙密度每增加1%有关的危险比为1.10(95%的可信区间为1.01-1.20),同时我们还表明间隙密度和疾病的持续时间有关,Spearman关联系数为0.44, $P = 0.004$ ^[37]。

Li等^[38]在靶向活检病理检测之前,先用CLE对43例传统结肠镜下非活动期UC患者进行炎症活动性评估,根据内镜图像下隐窝形态结构分为4个炎症等级,C、D级代表活动期炎症反应,而后分析上述分级标准与UC患者在后期随访中疾病复发的关系,结果表明内镜图像显示C、D等级炎症反应预测疾病复发的敏感性、特异性、准确性分别为64%、88.9%、74.4%,我们认为CLE在预测UC患者疾病复发方面的可靠性,可以和传统的金标准病理组织学结果相比^[39]。

近年来UC患者的治疗目标不仅仅局限于症状消失及控制疾病的活动性,组织学水平的黏膜愈合成为重要的治疗终点^[40-43]。在UC患者组织学愈合意味着没有残留的黏膜炎症、隐窝结构扭曲或萎缩等明显改变^[44],在进行内镜检查时,CLE能够观察到炎症细胞浸润、隐窝及血管结构紊乱,因此能够在体评估UC患者组织病理学水平的黏膜愈合,是实时评估UC患者组织学愈合的一种可靠工具^[45]。研究^[46-48]表明,组织学愈合可使UC患者的临床结果改善,与持续的临床缓解、住院及手术率的减少、疾病花费减低有关^[40,49-51],同时组织学水平的发现在疾病复发的预测中也有着重要作用,急性炎症细胞浸润比无细胞浸润更容易复发^[52]。

4 结论

CLE可无损伤由表及里地显示组织横断面的微观结构,作为实时模拟组织病理学诊断的一种新型内镜成像技术,革命性的改变了我们对UC患者的诊断及治疗思维,运用CLE,我们能够更高效地发现UC相关病变及预测复发,并指导

我们做出正确的干预措施以提高患者的预后。CLE使一些疾病的内镜诊断和病理组织学诊断有效地结合起来, 可以指导靶向活检以避免大量的无效活检带来的多种并发症, 并在将来有望取代耗时费力的传统组织病理切片技术。在以后的临床应用, 我们需要更多的多中心的研究来评估CLE这项技术在UC患者检查中的成本效益, 在UC患者复杂的临床背景下, CLE作为一种新的显像模式有望得到很好的应用。

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应用要点

运用CLE, 我们能够更高效地发现UC相关病变及预测复发, 并指导我们做出正确的干预措施以提高患者的预后。

■ 名词解释

共聚焦激光显微内镜(CLE): 共聚焦显微内镜及内窥镜技术的集合, 通过特殊荧光剂在不同组织中分布差异的特性, 在内镜检查的同时使用激光激发无创伤的产生人体局部组织学图像的装置。

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同行评价

本文就CLE在UC中的研究应用进行综述。CLE新设备在行常规内镜检查的同时,可以无创地实现实时在体组织病理学水平的检查,达到“虚拟活检”的目的,革命性的改变了我们对UC患者的诊断及治疗思维。本文对临床有一定指导价值。

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