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血清 MUC1、SCD-1、NLRP3 在溃疡性结肠炎患者中的表达 与凝血功能异常的相关性*

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摘要 目的:探讨与分析血清粘蛋白 1(MUC1)、硬脂酰辅酶 A 脱氢酶-1(SCD-1)、含 NLR 家族 PYRIN 域蛋白 3(NLRP3)在溃疡性结肠炎患者中的表达与凝血功能异常的相关性。**方法:**2019 年 8 月到 2021 年 7 月选择在本院诊治的溃疡性结肠炎患者 78 例作为病例组(包括轻度组患者 50 例与中重度组患者 28 例),同期选择在本院进行体检的健康人员 78 例作为对照组,检测三组血清 MUC1、SCD-1、NLRP3 水平与凝血指标,同时进行相关性分析与影响因素分析。**结果:**三组的血小板计数(PLT)、平均血小板体积(MPV)、血红蛋白(HGB)对比无差异($P>0.05$)。中重度组与轻度组的血清 MUC1、SCD-1、NLRP3 含量高于对照组,中重度组高于轻度组($P<0.05$)。中重度组与轻度组的部分凝血活酶时间(APTT)、凝血酶原时间(PT)低于对照组,纤维蛋白原(FIB)高于对照组,中重度组与轻度组对比也存在差异($P<0.05$)。在病例组中,Pearson 分析显示血清 MUC1、SCD-1、NLRP3 表达水平与凝血指标存在相关性($P<0.05$)。Logistic 多元回归方程显示 MUC1、SCD-1、NLRP3 等均为影响患者病情活动度的重要因素($P<0.05$)。**结论:**溃疡性结肠炎患者多伴随有血清 MUC1、SCD-1、NLRP3 的高表达,也多伴随有凝血功能异常,MUC1、SCD-1、NLRP3 表达与凝血功能异常存在相关性,也是影响患者病情活动度的重要因素。

关键词:溃疡性结肠炎;硬脂酰辅酶 A 脱氢酶-1;NLRP3 炎症小体;粘蛋白 1

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Correlation between the Expression of Serum MUC1, SCD-1 and NLRP3 in Patients with Ulcerative Colitis and Abnormal Coagulation Function*

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ABSTRACT Objective: To investigate and analysis the serum mucin 1 (MUC1), stearoyl-CoA desaturase-1 (SCD-1), NLR family PYRIN domain protein 3 (NLRP3) in patients with ulcerative colitis with abnormal coagulation function. **Methods:** From August 2019 to July 2021, 78 cases of patients with ulcerative colitis diagnosed and treated in our hospital were selected as the case group (included 50 patients in the mild group and 28 patients in the moderate-severe group), and the other 78 cases of healthy people who underwent physical examination were used as the control group. The serum levels of MUC1, SCD-1, NLRP3 and coagulation indexes were detected in the three groups, and correlation analysis and influencing factor analysis were carried out at the same time. **Results:** There were no significant difference in platelet count (PLT), mean platelet volume (MPV), and hemoglobin (HGB) compared among the three groups ($P>0.05$). The serum levels of MUC1, SCD-1 and NLRP3 in the moderate-severe group and the mild group were higher than those in the control group, and the moderate-severe group were higher than the mild group ($P<0.05$). The partial thromboplastin time (APTT) and prothrombin time (PT) in the moderate-severe group and the mild group were lower than those in the control group, and fibrinogen (FIB) were higher than that in the control group ($P<0.05$), the difference between moderate-severe group and mild group were also statistically significant ($P<0.05$). In the case group, Pearson analysis showed that serum MUC1, SCD-1, NLRP3 expression levels were correlated with coagulation indexes ($P<0.05$); Logistic multiple regression equation showed that MUC1, SCD-1, NLRP3, etc were important factors affected the patient's disease activity ($P<0.05$). **Conclusion:** Ulcerative colitis patients are often accompanied by high expression of serum MUC1, SCD-1, NLRP3, and are often accompanied by abnormal coagulation function. The expressions of MUC1, SCD-1 and NLRP3 are correlated with abnormal coagulation function, and are also important factors affecting the disease activity of patients.

Key words: Ulcerative colitis; Stearoyl-CoA dehydrogenase-1; NLRP3 inflammasome; Mucin 1

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前言

溃疡性结肠炎(Ulcerative colitis, UC)为临床上比较常见的炎症性肠病(Inflammatory bowel disease, IBD),主要发生部位为直肠与结肠,也是自身免疫有关的疾病^[1]。在临床上,溃疡性结肠炎主要表现为黏液脓血便、腹痛、腹泻等,具有易复发、进展慢、病情反复、病程长等特点,且发病率逐年上升,目前尚无根治方法^[2]。特别是溃疡性结肠炎患者的肠道炎症反复发作刺激肠道组织,可导致结直肠恶性肿瘤的发生,特别结直肠癌患者的死亡人数中有 10.0 %左右有溃疡性结肠炎病史^[3]。溃疡性结肠炎的具体发病机制还不明确,可能与环境、肠道菌群、免疫失调等存在相关性,特别是炎症因子、凝血功能与溃疡性结肠炎息息相关^[4]。溃疡性结肠炎患者的局部肠黏膜中微血栓阳性率在 30.0 %以上,故推测凝血指标可能与疾病活动有关^[5]。粘蛋白 1(Mucin 1, MUC1)在溃疡性结肠炎患者中的表达异常,也与肿瘤、炎症的发生存在相关性。硬脂酰辅酶 A 脱氢酶-1(Stearoyl-CoA desaturase-1, SCD-1)是一种脂质过氧化指标,参与炎症感染、免疫反应等^[6,7]。炎症小体为主要识别不同损伤信号的蛋白质复合物,NLR 家族 PYRIN 域蛋白(NLR family PYRIN domain-containing protein, NLRP)是炎症小体的关键组成部分,目前研究最多的是 NLRP3^[8]。本文具体探讨了血清 MUC1、SCD-1、NLRP3 在溃疡性结肠炎患者中的表达与凝血功能异常的相关性。

1 资料与方法

1.1 研究对象

2019 年 8 月到 2021 年 7 月选择在新疆维吾尔自治区人民医院诊治的溃疡性结肠炎患者 78 例作为病例组,采用改良 Mayo 评分系统对溃疡性结肠炎活动度进行判定,即轻度活动(≤ 5 分,轻度组, $n=50$)及中重度活动(≥ 6 分,中重度组, $n=28$),同期选择在本院体检的健康人员 78 例作为对照组。

纳入标准:本院伦理委员会批准了此次研究;所有入选者知情同意本研究;病例组符合溃疡性结肠炎的诊断标准;小学

及其以上文化水平;入院检测前未给予任何治疗。

排除标准:病情危重患者;伴有严重精神障碍患者;伴有恶性肿瘤患者;哺乳或妊娠期妇女;合并传染性疾病者;既往消化道切除史的患者;伴随有血液系统疾病者;伴随有心脑血管疾病者。

1.2 血清 MUC1、SCD-1、NLRP3 检测

取所有入选者的空腹静脉血 2-3 mL,不抗凝,4℃放置 <1 周,3000 rpm 离心 10 min,取上层血清。采用酶联免疫吸附法检测血清 MUC1、NLRP3 含量,采用液相色谱-质谱法检测血清 SCD-1 含量,检测试剂盒购自上海宸功生物技术有限公司与北京博奥生物技术有限公司。

1.3 凝血指标检测

取 1.2 中的血液样本,加入 0.2 mL 枸橼酸钠抗凝管中,4℃放置 <1 周,3000 rpm 离心 10 min,离心半径 15 cm,分离上层血浆,采用全自动生化分析仪(日本日立公司 87914 型)检测凝血酶原时间(Prothrombin time, PT)、人部分凝血活酶时间(Activated partial thromboplastin time, APTT)、纤维蛋白原(Fibrinogen, FIB),检测试剂盒购自南京基蛋生物科技有限公司试剂盒。

同时检测与记录所有患者的相关血常规指标,包括血小板计数(Platelet count, PLT)、平均血小板体积(Mean platelet volume, MPV)、血红蛋白(Hemoglobin, HGB)等。

1.4 统计方法

本次研究统计软件为 SPSS22.00 统计学软件, $P < 0.05$ 为差异有统计学意义。计量资料结果以($\bar{x} \pm s$)差表示,多组间采用方差分析,两组间采用 LSD;计数数据采用 $n(\%)$ 表示,采用卡方 χ^2 检验与方差分析,采用 Pearson 进行相关性分析,以 Logistic 多元回归方程进行多因素分析。

2 结果

2.1 基础资料对比分析

三组一般资料对比无差异($P > 0.05$),中重度组的 Mayo 内镜评分与总体评分都高于轻度组($P < 0.05$)。见表 1。

表 1 三组基础资料对比分析

Table 1 Comparative analysis of basic data of the three groups

Groups	n	Gender (Male/female)	Age (years)	Body mass index (kg/m ²)	Mayo Endoscopy Score (score)	Mayo Overall Score (score)
Moderate severe group	28	15/13	49.52±5.15	22.48±0.24	2.54±0.24	9.17±0.87
Mild group	50	26/24	49.82±4.12	22.87±1.42	1.59±0.27	4.09±0.33
Matched group	78	40/38	49.16±3.33	22.19±0.98		

2.2 血常规指标对比

三组的 PLT、HGB 与 MPV 对比无差异($P > 0.05$)。见表 2。

2.3 血清 MUC1、SCD-1、NLRP3 含量对比

中重度组与轻度组的血清 MUC1、SCD-1、NLRP3 含量高于对照组,中重度组高于轻度组($P < 0.05$)。见表 3。

2.4 凝血指标对比

中重度组与轻度组的 APTT、PT 低于对照组, FIB 高于对照组,中重度组与轻度组对比有差异($P < 0.05$)。见表 4。

2.5 相关性分析

在病例组中, Pearson 分析显示血清 MUC1、SCD-1、NLRP3 表达水平与凝血指标存在相关性($P < 0.05$)。见表 5。

2.6 影响因素分析

在病例组中, Logistic 多元回归方程显示 MUC1、SCD-1、NLRP3 等都为影响患者病情活动度的重要因素($P < 0.05$)。见表 6。

表 2 三组血常规指标对比(均数±标准差)

Table 2 Comparison of routine blood indexes among the three groups (mean ± standard deviation)

Groups	n	PLT($\times 10^9/L$)	HGB(g/L)	MPV(fL)
Moderate severe group	28	234.01±15.02	128.48±24.75	10.33±0.24
Mild group	50	234.98±14.20	128.77±16.20	10.24±0.18
Matched group	78	234.52±19.02	128.03±19.10	10.30±0.16
F		0.295	0.333	0.135
P		0.801	0.722	0.878

表 3 三组血清 MUC1、SCD-1、NLRP3 含量对比(均数±标准差)

Table 3 Comparison of MUC1, SCD-1 and NLRP3 contents in serum of the three groups (mean ± standard deviation)

Groups	n	MUC1(U/mL)	SCD-1(mmol/L)	NLRP3(pg/mL)
Moderate severe group	28	8.99±0.24 ^{ab}	7.28±0.13 ^{ab}	29.81±2.41 ^{ab}
Mild group	50	4.29±0.19 ^a	5.02±0.28 ^a	14.09±0.98 ^a
Matched group	78	0.78±0.09	1.38±0.09	7.38±0.47
F		19.001	26.703	21.752
P		<0.001	<0.001	<0.001

Note: Compared with matched group, ^a $P<0.05$; Compared with mild group, ^b $P<0.05$, the same below.

表 4 三组凝血指标对比(均数±标准差)

Table 4 Comparison of coagulation indicators among the three groups (mean ± standard deviation)

Groups	n	APTT(s)	PT(s)	FIB(g/L)
Moderate severe group	28	28.40±2.19 ^{ab}	8.59±0.66 ^{ab}	4.26±0.24 ^{ab}
Mild group	50	30.20±1.58 ^a	10.88±0.18 ^a	3.84±0.32 ^a
Matched group	78	32.99±0.49	12.88±1.04	3.17±0.28
F		12.013	14.444	9.132
P		<0.001	<0.001	0.002

表 5 血清 MUC1、SCD-1、NLRP3 在溃疡性结肠炎患者中的表达与凝血功能异常的相关性(n=78)

Table 5 Correlation between expression of MUC1, SCD-1 and NLRP3 in serum and coagulation dysfunction in patients with ulcerative colitis (n=78)

Indexs	APTT	PT	FIB
MUC1-r	-0.525	-0.555	0.577
P	0.000	0.000	0.000
SCD-1-r	-0.601	-0.633	0.613
P	0.000	0.000	0.000
NLRP3-r	-0.597	-0.522	0.624
P	0.000	0.000	0.000

表 6 影响溃疡性结肠炎患者病情活动度的 Logistic 多元回归方程分析(n=78)

Table 6 Logistic multiple regression equation analysis of disease activity in patients with ulcerative colitis (n=78)

Indexs	β	SE	Wald	P	OR	95%CI
MUC1	0.572	0.089	41.489	0.011	1.782	1.288-1.842
SCD-1	0.562	0.074	57.103	0.019	1.824	1.658-1.993
NLRP3	0.403	0.103	14.444	0.021	1.149	1.092-1.451

3 讨论

溃疡性结肠炎是炎症性肠病种类之一,常反复发作,严重时可同时伴有皮肤黏膜等肠外表现,对患者生活质量产生严重影响^[9]。多数溃疡性结肠炎患者存在慢性复发性炎症,病程越长,易形成血栓,增加癌变风险。在溃疡性结肠炎患者中,血栓形成发生率约为5.0%,严重时危及生命,是导致溃疡性结肠炎死亡主要原因之一^[10,11]。

溃疡性结肠炎的病因机制尚未清楚,其发病率呈不断上升趋势,病变部位多位于直肠和乙状结肠,以溃疡为主^[12]。本研究显示:中重度组与轻度组的血清 MUC1、SCD-1、NLRP3 含量高于对照组,中重度组高于轻度组,表明溃疡性结肠炎患者多表现为血清 MUC1、SCD-1、NLRP3 的高表达,且与患者的病情存在相关性。该结果与 Kvorjak M 等人^[13]以及明兰等人^[14]的报道具有相似性。分析可知,MUC1 为黏蛋白的主要类型之一,可调节多种信号通路,可维持肠道内环境的稳定,还可影响细胞的增殖和凋亡^[15]。MUC1 高表达可导致肠道形成易感环境,进而引发炎症性相关疾病。机体免疫功能紊乱是溃疡性结肠炎的重要因素之一,血清中的 SCD-1 是炎症反应的重要指标,可参与溃疡性结肠炎的发生及发展过程^[16]。NLRP3 的高表达可参与调节胞内钾离子外流、活性氧、结晶、微生物毒素等过程,还可引起炎症反应的发生。特别是在溃疡性结肠炎的发病进展中,血小板明显活化,与 NLRP3 炎症小体活化也存在相关性^[17,18]。

溃疡性结肠炎是一组多病因引起的、异常免疫介导的肠道慢性及复发性炎症,多数患者存在高凝状态,表现为形成微血栓形成、微循环出现障碍,将会导致病情恶化^[19]。特别是肠黏膜微血栓形成会致使肠黏膜溃疡,并伴有缺血坏死,加重结直肠黏膜的病变,诱发结直肠癌的发生^[20]。本研究显示中重度组与轻度组的 APTT、PT 低于对照组,FIB 高于对照组,中重度组与轻度组对比有差异,表明溃疡性结肠炎患者多伴随有凝血功能异常。该结果与 Bai X 等人^[21]的报道具有相似性。分析可知,肠道炎症反应会刺激 FIB 高表达,使得 FIB 局部粘附及聚集,促进炎症细胞趋化,并诱发氧自由基,使得肠道内皮细胞受到损伤,导致肠道炎症反应加重,导致患者病情恶化^[22]。PT、APTT 分别反映外、内源性凝血系统状况,PT、APTT 降低表明机体存在血栓性疾病,且伴随有血液高凝状态。同时 APTT、PT 降低可增加血液粘滞性、外周阻力,促进血栓形成与血小板聚集^[23]。

溃疡性结肠炎临床特点为反复发作的腹痛、腹泻、黏液血便,其病因及发病机制尚不明确,但 APTT、PT、FIB 可作为炎症活动程度的预测指标,特别是当炎症反应发展到一定程度时,将会形成微血栓、溃疡等,进一步导致肠道黏膜缺血坏死,肠道病变加重,导致恶性循环^[24]。本研究 Pearson 分析显示溃疡性结肠炎患者的血清 MUC1、SCD-1、NLRP3 表达水平与凝血指标存在相关性;Logistic 多元回归方程显示 MUC1、SCD-1、NLRP3 等都是影响患者病情活动度的重要因素。该结果与蒋志滨等人^[25]以及等人 Zhang F^[26]的报道具有相似性。分析可知,MUC1 基因在大多数上皮细胞中都处于微量表达状况,若 MUC1 表达水平升高,可通过信号通路的调节,可促进结直肠炎症的发生^[27]。有研究显示在溃疡性结肠炎和结直肠癌组织中,MUC1 的表达量升高,且糖基化程度出现降低,可参与患者

的病情发展过程。SCD-1 含量增加将导致体内游离的脂肪酸过高,导致黏膜损伤加剧溃疡性结肠炎的发展,还可使机体一直处在高凝状态,血管发生痉挛^[28]。如果抑制体内过氧化脂质的生成,可降低血清中的 SCD-1 水平,可改善患者的病情状况。NLRP3 在炎症、纤维化、肿瘤等发生发展中具有重要作用,其中 NLRP3 炎症小体的激活因素比较多,其表达激活后可促进白细胞介素-1 β 等炎症因子的成熟和分泌,引起组织损伤与炎症级联反应,使得患者肠上皮完整性破坏,影响患者的预后^[29]。也表明治疗溃疡性结肠炎不仅应重视 MUC1、SCD-1、NLRP3 的控制,亦应关注患者凝血指标变化,从而预防溃疡性结肠炎病情恶化,改善患者的预后^[30]。但因经费限制,本次研究纳入患者数量较少,未进行预测价值分析,凝血指标也较少,将在后续研究中探讨。

总之,溃疡性结肠炎患者多伴随有血清 MUC1、SCD-1、NLRP3 的高表达,也多伴随有凝血功能异常,MUC1、SCD-1、NLRP3 表达与凝血功能异常存在相关性,也是影响患者病情活动度的重要因素。

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(上接第 2685 页)

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