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### Shijie Huaren Xiaohua Zazhi

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# 溃疡性结肠炎并发下肢动脉血栓: 一例报道及文献复习

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## Ulcerative colitis complicated with lower extremity arterial thrombosis: A case report and review of the literature

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## Abstract

### BACKGROUND

Thromboembolic disease (TED) is one of the extra-intestinal manifestations of ulcerative colitis (UC). Deep venous thrombosis in the lower limbs and pulmonary embolism are common in clinical practice, although embolism can also occur in other organs such as the cerebrum, kidney, and liver. However, arterial TED, mainly occurring in the mesenteric artery, is rare. Despite evidence that there is a real connection between ATED and UC, controversy exists over the relationship between ATED and inflammatory bowel disease.

### CASE SUMMARY

A 63-year-old female patient was diagnosed with UC in 2014. She was initially treated with salazopyridine, which was then switched to mesalazine for long-term maintenance treatment, and his condition was stable. In April 2017, her UC was active again, and the symptoms were relieved after treatment with prednisone. Prednisone treatment was discontinued 2 mo later, and the maintenance treatment with mesalazine continued. At this time, her platelet count was elevated but no attention was paid. After that, the patient did not come to the hospital regularly for follow-up, during which there was an aggravation of bloody diarrhea, and she took prednisone irregularly. Six months later, the patient suddenly presented pain in the left lower limb with local necrosis of the toe, and the platelet count was as high as  $735 \times 10^9/L$ . Lower limb CT angiography showed no filling of contrast agent in the lumen of the left popliteal artery and the upper end of the left tibial anterior, tibial posterior, and peroneal arteries, and the lumen of the left tibial anterior, tibial posterior, and middle and distal peroneal arteries. A diagnosis of UC with left lower limb arterial embolism was made. Left lower limb artery



thrombectomy was performed, but left foot dorsal and toe necrosis was not improved. After left foot toe amputation, multiple left foot debridements, and skin grafting, her symptoms were controlled.

## CONCLUSION

Lower limb arterial thrombosis may be associated with active UC. Once happened, it will lead to serious and even life-threatening complications. During the treatment of UC, platelet count and coagulopathy should be closely monitored so that timely intervention could be given.

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Key Words: Ulcerative colitis; Lower extremity arterial thrombosis; Inflammatory bowel disease; Thrombocytosis

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## 摘要

### 背景

血栓栓塞性疾病(thromboembolic disease, TED)是溃疡性结肠炎(ulcerative colitis, UC)的肠外表现之一,但是临床上常见的是下肢深静脉血栓和肺栓塞,其他部位如大脑、肾、肝、肠系膜静脉等也可发生栓塞,动脉TED较为少见,而且多发于肠系膜动脉。虽然有证据表明两者之间存在真正的关联,但在大规模队列研究中,人们对ATED与炎症性肠病之间的关联并没有达成共识。

### 病例概述

63岁女性患者, 体型正常, 既往体健, 无高血压糖尿病冠心病等病史, 无手术病史, 无烟酒等不良嗜好。2014年诊断UC, 初使用柳氮磺吡啶1.0 tid, 后换成美沙拉嗪(莎尔福1.0 tid)长期维持治疗, 病情稳定。2017-04病情再次活动, 加用糖皮质激素治疗后症状缓解, 逐步减量使用强的松, 2 mo后停用强的松, 继续莎尔福1.0 tid维持治疗, 此时发现血小板计数偏高, 但未加以重视。之后患者并未定期来院随访, 期间有腹泻血便加重现象, 自行不规则服用强的松。6 mo后患者突然出现左下肢疼痛伴脚趾局部坏死, 血小板计数高达 $735 \times 10^9/L$ , 下肢血管CT血管造影显示左侧腘动脉及左侧胫前、胫后动脉、腓动脉上端管腔未见造影剂充盈, 左侧胫前、胫后动脉、腓动脉中远段管腔变细。诊断UC合并左下肢动脉血栓。行左下肢动脉取栓术, 但仍不能改善左足背和脚趾坏死症状, 又行左足1-5趾截断术、多次左足扩创术以及植皮手术, 症状才得以控制。

## 结论

下肢动脉血栓可能与UC活动有关, 一旦发生, 会导致严重并发症, 严重时危及生命。在治疗UC的同时, 要警惕血小板计数升高及凝血异常的现象, 及时干预并密切随访。

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关键词: 溃疡性结肠炎; 下肢动脉血栓形成; 炎症性肠病; 血小板增多

**核心提要:** 本文介绍一例极少见的并发下肢动脉血栓的溃疡性结肠炎病例, 分享其病情衍变和治疗过程, 并复习了炎症性肠病(inflammatory bowel disease, IBD)和血栓栓塞性疾病(thromboembolic disease, TED)相关性分析的一些文献。旨在引起医生对TED风险的认识, 说明在诊治IBD时及时发现和处理血栓并发症非常重要。

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## 0 引言

炎症性肠病(inflammatory bowel disease, IBD)有多种肠外表现, 血栓栓塞性疾病(thromboembolic disease, TED)是其一, 但多以静脉血栓或肺栓塞为主, 下肢动脉血栓及其少见, 但往往会引起严重后果, 期待临床医生及早发现, 及早干预, 以减少致残和死亡的风险。

## 1 病例报告

患者, 陈某, 女, 63岁, 正常体型。既往体健, 无高血压糖尿病冠心病等病史, 无手术病史, 无烟酒等不良嗜好。2014年因“反复粘液血便2 mo余”, 诊断溃疡性结肠炎, 初使用柳氮磺吡啶1.0 tid, 后换成美沙拉嗪(莎尔福1.0 tid)长期维持, 病情较稳定(图1)。2017-04因再次出现“频繁粘液血便1 wk伴腹痛”考虑病情活动(图2), 加用强的松20 mg qd, 病情控制后逐步减量, 2017-06停强的松, 继续使用美沙拉嗪(莎尔福1.0 tid)维持治疗。期间发现血小板升高( $431 \times 10^9/L$ ), 未加以重视, 之后未定期门诊随访, 大便次数2-4次/d, 偶尔因大便次数多自行服用强的松2片, 无发热消瘦腹痛等不适。2017-11突然因“突发左下肢疼痛1 wk伴脚趾局部坏死”入院, 此时血小板计数达 $735 \times 10^9/L$ , 凝血功能提示血管性血友病因子(von Willebrand Factor, vWF)210%, D-D聚体 $2.5 \mu g/mL$ , 均较正常值升高。下肢CTA示左侧腘动脉及左侧胫前、胫后动脉、腓动脉上端管腔未见造影剂充盈, 左侧胫前、胫后



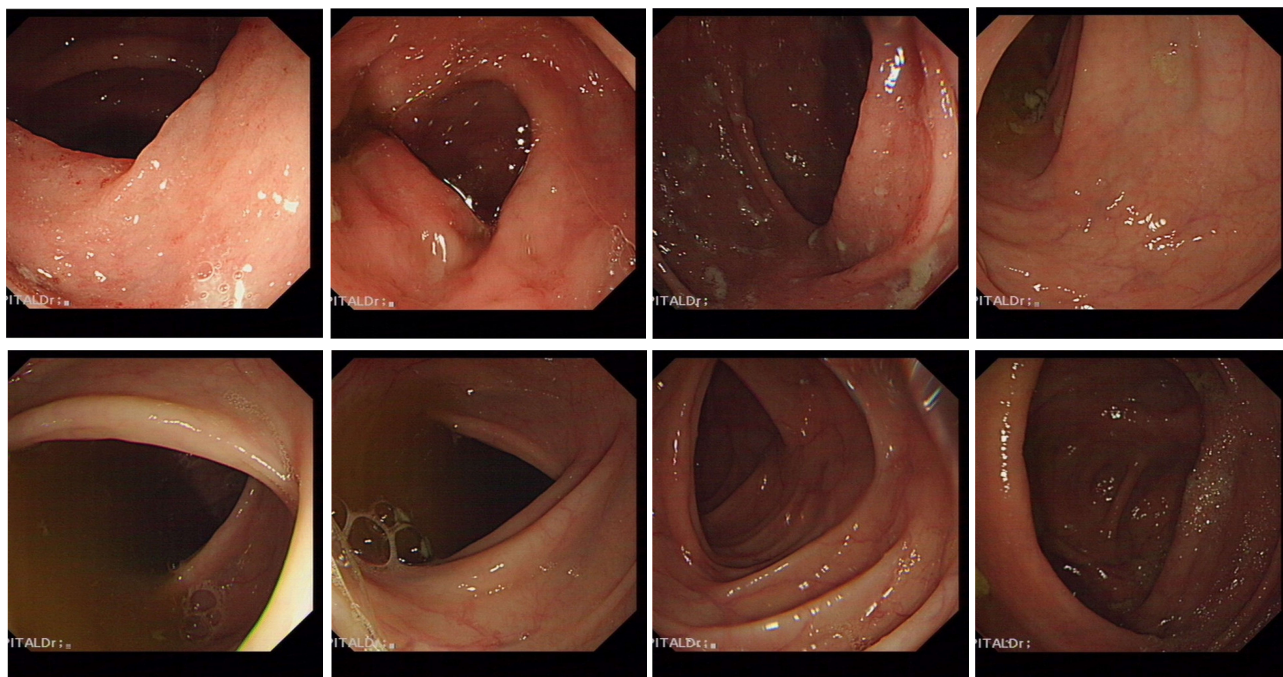


图 1 2015-8-24 内镜下所见: 直肠、乙状结肠、降结肠黏膜水肿, 呈细颗粒样改变, 有脓性分泌物附着, 无明显糜烂, 无自发性出血和接触性出血, 横结肠、升结肠、回盲部黏膜正常。

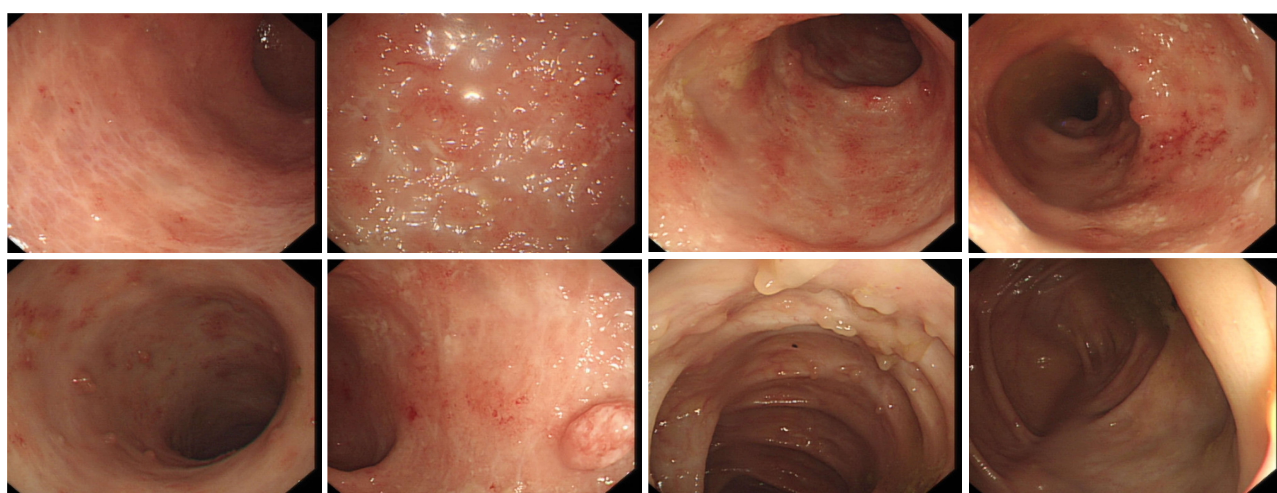


图 2 2017-4-24 内镜下所见: 直肠、乙状结肠、降结肠、横结肠黏膜水肿, 颗粒样改变, 部分黏膜糜烂, 可见红斑, 质脆, 接触性出血, 升结肠有炎症息肉样改变, 回盲部黏膜正常。

动脉、腓动脉中远段管腔变细(图3)。

## 2 最后诊断

左下肢动脉栓塞和血栓形成(左侧腘动脉, 左侧胫前、胫后动脉, 腓动脉上端管腔), 溃疡性结肠炎(慢性复发型, 轻度活动期, 左半结肠为主)。

## 3 治疗

给予西洛他唑100 mg *bid*治疗, 并行左下肢动脉取栓术(左侧股总动脉取出长约15 cm血栓, 股深动脉取出散

碎栓子), 术后左下肢疼痛逐步缓解, 但左足背及脚趾持续坏死, 又于2017-11-14行左足扩创+负压封闭吸引技术(vacuum sealing drainage, VSD)+1-5趾截断术, 后又因创面修复不良, 分别于2017-11-23行左足扩创+VSD, 2017-11-29行左足扩创+VSD+植皮术。

## 4 结果和随访

术后左足疼痛缓解, 创面愈合, 继续服用西洛他唑100 mg *bid*和美沙拉嗪1.0 *tid*, 凝血功能检查(2018-03)示vWF190%、D-D聚体0.85  $\mu\text{g/mL}$ , 血小板计数逐步下降恢复正常后停



表 1 炎症性肠病患者血栓栓塞并发症的处理

血栓栓塞并发症的一级预防	
门诊患者	住院患者
一般措施	一般措施
医生意识	疾病活动改善
病人教育	早期动员
积极的疾病治疗和缓解维持	导管的明智使用
识别、消除或修改危险因素	恢复脱水或营养不良
类固醇使用	用药修改
吸烟	围手术期或严重的非手术病人预防性抗凝(普通肝素或低分子肝素)
口服避孕药	当血栓形成风险增加或仅当抗凝血禁忌症伴高出血风险时, 加机械措施
心血管危险因素和其他合并症	
长时间飞行	
弹力袜?	
治疗血栓栓塞事件	
改善疾病活动	
血液病科会诊和血栓性血友病筛查	
治疗性抗凝(普通肝素或低分子肝素)	
溶栓-介入放射学/外科会诊	
血栓栓塞并发症的二级预防	
在一次血栓栓塞事件发作之后	
活动性疾病-自发性事件	
短期内抗凝治疗? 3-6 mo	
在随后的疾病发作时加上抗凝剂?	
非活动期的疾病-自发性事件	
长期抗凝治疗?	
复发性TE或遗传性血栓性血友病	
血液病科会诊	
长期抗凝	

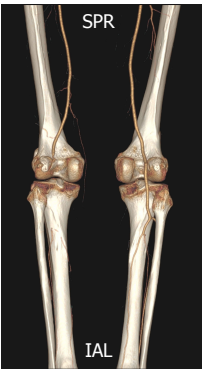


图 3 左侧腘动脉及左侧胫前、胫后动脉、腓动脉上端管腔未见造影剂充盈, 左侧胫前、胫后动脉、腓动脉中远段管腔变细。

用西洛他唑, 并继续使用美沙拉嗪1.0 *tid*维持治疗。目前随访15 mo, 未再发生新的血栓事件, 血小板计数持续正常。溃疡性结肠炎症状稳定(图4)。

5 讨论

溃疡性结肠炎是IBD两个临床类型之一, 隶属于自身免

疫系统疾病, 病因不明, 除了肠道表现外, 还可以有一系列的肠外表现。常见有肠外表现有皮肤、黏膜、关节、眼、肝胆疾病、血栓TED等。可能出现中毒性巨结肠、肠穿孔、下消化道出血、上皮内瘤变以及癌变等并发症。以往我们临床医生对血栓TED缺乏认识, 但是随诊近年来IBD发病率的升高, 临床医生对IBD疾病的认识以及诊治经验的积累, 我们已经发现血栓TED是IBD的一项严重并发症。但是临床上常见的是下肢深静脉血栓和肺栓塞<sup>[1]</sup>(90.4%), 其他部位如大脑、肾、肝、肠系膜静脉等也可发生栓塞<sup>[2-4]</sup>。动脉血栓TED非常罕见, 目前的文献多见于一些零星的病例报道, 可能涉及脑、视网膜、颈动脉、冠状动脉、内脏、髂、肾、上下肢体动脉或主动管的血栓形成和/或闭塞。通常在介入或外科手术后更为常见, 但也可能自发发生<sup>[5]</sup>。虽然有证据表明两者之间存在真正的关联<sup>[6]</sup>, 但在大规模队列研究中, 人们对ATED与IBD之间的关联并没有达成共识<sup>[7]</sup>。ATED发病率最高的是肠系膜缺血, 其风险是对照组的3.5倍<sup>[5]</sup>。就冠状动脉疾病、缺血性心脏病和心肌梗死而言, 多



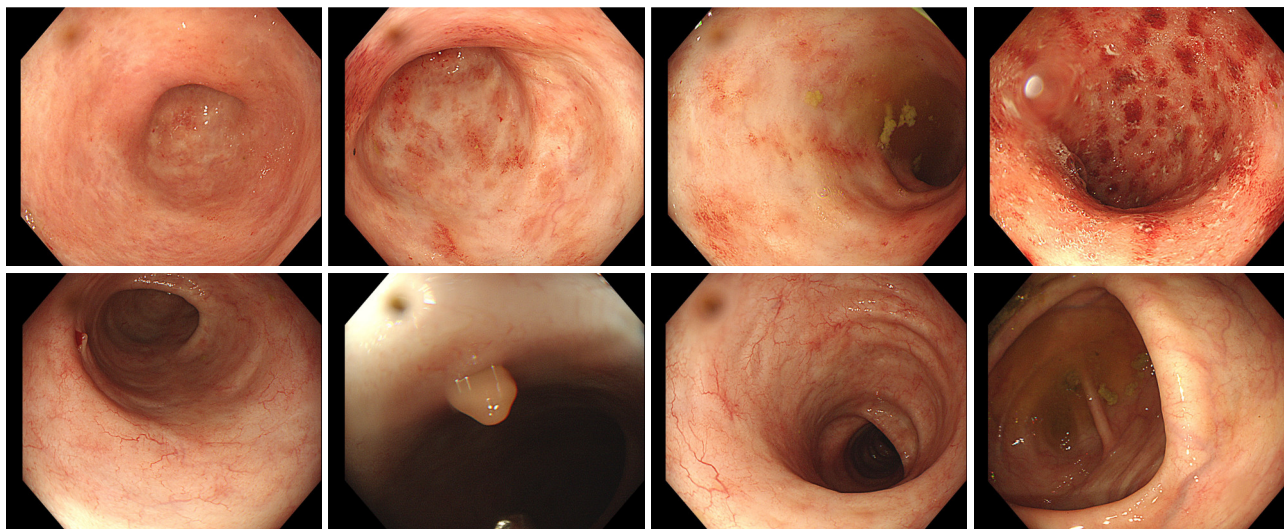


图 4 2019-03-08 内镜下所见: 黏膜病损改善, 呈治疗后改变, 直肠、乙状结肠、降结肠黏膜可见疤痕形成, 血管网模糊, 横结肠脾区可见黏膜红斑, 无接触性出血, 横结肠肝曲有一枚息肉增生, 活检夹除: 病理示增生性息肉, 升结肠及回盲部黏膜正常。

份研究报告显示<sup>[6,8-12]</sup>, 患病风险比对照组高1.22-2.85之间。唯一一项研究回顾了住院IBD患者与周围血管疾病(peripheral vascular disease, PVD)的关系发现IBD与PVD的发展呈反比关系<sup>[13]</sup>。下肢动脉血栓的报道比较少见, 北京协和医院报道的13例IBD并发血栓事件中仅有1例是下肢动脉血栓<sup>[14]</sup>。

目前我们已发现多种导致ATE致病因素, 包括内皮功能障碍、炎症介导的动脉介质钙沉积、高同型半胱氨酸(homocysteine, Hcy)血症、血小板活化、凝血和纤溶改变。活动期IBD患者可能会造成体内抗凝与凝血系统失衡, 若未及时治疗, 体内凝血系统大量被激活, 可以导致微动脉和微静脉现象, 严重者大动脉和大静脉血栓可以形成。柳氮磺吡啶为二氢叶酸还原酶的抑制剂, 致叶酸缺乏, 形成高同型半胱氨酸血症, 血中Hcy浓度升高可直接或间接损伤血管内皮细胞(endothelial cells, EC)功能, 引起脂蛋白和胆固醇在血管壁沉积, 灭活一氧化氮, 激活血小板, 导致体内凝血系统失衡, 抑制纤溶系统, 促进动脉粥样硬化和血栓形成<sup>[15,16]</sup>。糖皮质激素可对EC有损伤, 促进血小板释放大血小板源性微粒, 可以激活和启动内、外源性凝血途径, 降低纤维蛋白溶解能力, 造成血液处于高凝状态, 促进血栓性疾病发生<sup>[17]</sup>。

对于IBD患者血栓栓塞的治疗包括首次血栓栓塞并发症的一级预防、血栓栓塞并发症的治疗和血栓栓塞并发症复发的二级预防(表1)<sup>[5]</sup>。目前我国已经制定了《中国住院IBD患者静脉血栓栓塞症防治的专家共识意见》, 但是国内外文献针对动脉血栓栓塞症均没有明确的指南性意见。

此例报道中患者既往无高血压、心脏病、糖尿病病史, 无吸烟饮酒肥胖高龄等高危因素。仅病程中有长

达5 mo血小板计数升高的病史, 但遗憾的是并没有得到干预。回顾分析: 该患者在发生下肢动脉血栓之前存在溃疡性结肠炎慢性活动, 糖皮质激素的不规则使用, 血小板进行性异常升高, 不得不考虑该患者下肢动脉血栓栓塞与其基础疾病溃疡性结肠炎有一定联系。经西洛他唑治疗, 左下肢动脉取栓以及维持西洛他唑治疗后目前血小板计数正常, 未再有新的血栓栓塞事件发生。

总之, 这个病例仅反应了一例溃疡性结肠炎患者同时合并下肢动脉血栓栓塞事件的发生。动脉血栓TED与IBD的关系仍需要大样本数据来明确。监测IBD患者的血小板计数, 重视IBD患者血液的高凝状态, 早期快速诊断及干预血栓栓塞性事件, 对于改善IBD患者预后及降低致残率、病死率有着十分重要的意义。

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