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溃疡性结肠炎伴继发性血小板增多症一例并文献复习

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摘 要

溃疡性结肠炎(UC)是一种病因不明的慢性肠道内炎症，随着生活水平的进步和环境污染的加重，UC的发病率较前大幅提高，大多患者腹痛、便血症状明显，严重影响了正常生活，已演变成一种全球性的负担。尽管目前内镜及组织学检查已经普及，诊断方式简单，治疗指南明确，但仍有相当一部分患者对药物治疗的反应不明显，极大地影响了患者的生活质量。所以在临床工作中对患者进行全面检查，多方面分析，减少误诊、实施个体化治疗显得尤为重要。最近我们接诊了一名溃疡性结肠炎伴血小板增多的患者，院外进行传统的溃结治疗效果不明显，在我院进行降血小板治疗后临床症状改善明显，血小板除了有止血作用，还作为传统的抗炎细胞在炎症性肠病中发挥作用，因此控制血小板数量也可有效控制肠道炎症的发展。此篇通过对我科收治的1例溃疡性结肠炎合并血小板增多症患者的诊治过程进行回顾性分析并文献复习，讨论异常血小板活化对肠道炎症的影响，考虑调节血小板治疗溃疡性结肠炎的潜在益处，为今后的治疗提供新的思路。

关键词

溃疡性结肠炎，血小板增多症，继发性血小板增多症，肠道炎症

One Case of Ulcerative Colitis with Secondary Thrombocytosis and Literature Review

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Abstract

Ulcerative colitis (UC) is a chronic intestinal inflammation with unknown etiology. With the improvement of living standards and the aggravation of environmental pollution, the incidence of UC has increased significantly. Most patients have obvious symptoms of abdominal pain and blood in the stool, which seriously affects their normal life and has become a global burden. Although endoscopy and histology have been widely used, with simple diagnostic methods and clear treatment guidelines, quite a few patients still do not respond significantly to drug therapy, which greatly affects the quality of life of patients. Therefore, in clinical work, it is particularly important to conduct comprehensive examination of patients, analyze in many aspects, reduce misdiagnosis and implement individualized treatment. Recently, we received a patient with ulcerative colitis accompanied by thrombocytosis. The effect of traditional ulcerative colitis treatment outside the hospital was not obvious, but the clinical symptoms improved significantly after the treatment of platelet lowering in our hospital. In addition to their role in hemostasis, platelets also play a role as traditional anti-inflammatory cells in inflammatory bowel disease, so controlling platelet count can also effectively control the development of intestinal inflammation. Controlling platelet count can also effectively control the development of intestinal inflammation. This paper retrospectively analyzed the diagnosis and treatment process of a patient with ulcerative colitis complicated with thrombocytosis admitted to our department and reviewed the literature, discussed the influence of abnormal platelet activation on intestinal inflammation, considered the potential benefits of platelet regulation in the treatment of ulcerative colitis, and provided new ideas for future treatment.

Keywords

Ulcerative Colitis, Thrombocytosis, Secondary Thrombocytosis, Intestinal Inflammation

1. 病例资料

患者男，31 岁，近 1 月来反复出现粘液脓血便，每日排便 4~5 次，偶有便血，伴有轻微下腹部不适，排便后可缓解，1 周前出现腹泻加重，每日大便 10 余次，伴有发热，于外院行结肠镜检查诊断溃疡性结肠炎，给予美沙拉嗪颗粒及抗生素治疗，症状无明显缓解。既往无特殊病史。入院查体：T：36.2℃ P：140 次/分 R：20 次/分 BP：108/74 mmHg。贫血貌，慢性病容，皮肤、黏膜及巩膜苍白，心率增快，心律规整，左下腹有轻压痛，无反跳痛，余未见明显阳性体征。入院后完善相关辅助检查：白细胞：24.99 × 10^9/L，红细胞：2.78 × 10^9/L，血红蛋白：68 g/L，血小板：1013 × 10^9/L，大便潜血实验阳性，大便细菌培养：大肠埃希氏菌 80%，变形杆菌 5%；大便难辨梭状芽孢杆菌毒素阴性；CMV、EBV、*C. diff* 均阴性；结核抗体、T-SPOT 均阴性。腹部 CT：结直肠壁增厚伴异常强化(图 1)。肠镜检查考虑溃疡性结肠炎活动期(图 2)。病理：粘膜充血、水肿，重度急慢性发炎，较多淋巴细胞、浆细胞及少量嗜酸性粒细胞浸润(图 3)。初步诊断为溃疡性结肠炎；白血病？考虑患者白细胞及血小板异常增高，请血液科会诊，行骨

髓穿刺活检，骨髓细胞图片提示感染样骨髓象，血小板增多，小细胞低色素性贫血(图 4)。活检结果提示骨髓增生程度大致正常，基因突变及染色体检查：骨髓 JAK-2、MPL、CALR 基因未检测到明确突变，BCR-ABL 融合基因为阴性。排除原发性血小板增多症，考虑为溃疡性结肠炎伴继发血小板增多症，肠道感染，重度贫血。给予甲泼尼龙静滴、美沙拉嗪颗粒口服、美沙拉嗪栓肛门给药、羟基脲口服、干扰素皮下注射、补蛋白、补液等对症支持治疗，2 周后患者症状明显好转，大便控制在 2~3 次/日，无明显粘液脓血，复查血常规：血红蛋白 75.0↓g/L，血小板计数 521↑10^9/L。再次行肠镜提示溃疡性结肠炎缓解期。

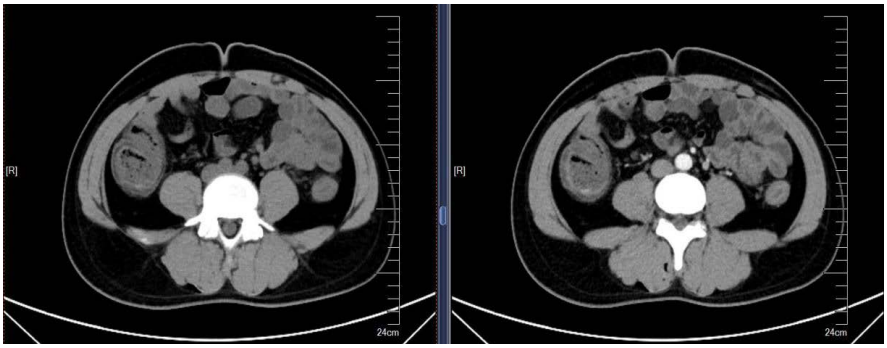

Figure 1. Abdominal CT scan shows intestinal wall thickening with abnormal enhancement
图 1. 腹部 CT 可见肠壁增厚并伴有异常强化

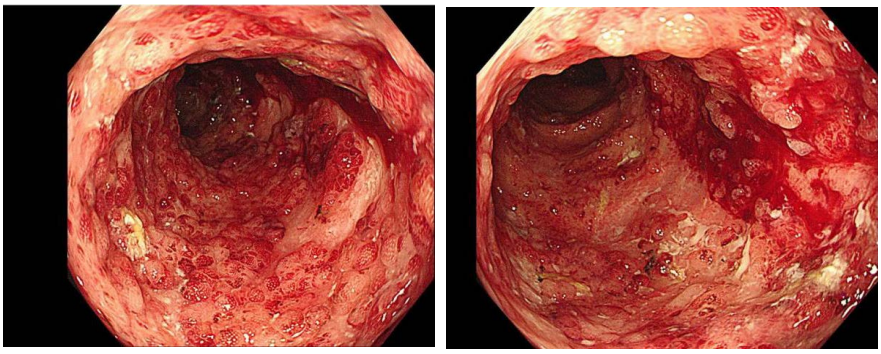

Figure 2. There are many superficial needle-like ulcers in the intestinal mucosa, covered with white moss. The mucosa looks like granules, the vascular texture is missing, the mucosa has a few deep ulcers, and there is active bleeding
图 2. 肠道粘膜广泛密布针尖样浅溃疡，有白苔覆盖，粘膜呈颗粒样改变，血管纹理消失，部分见深溃疡，有活动性出血

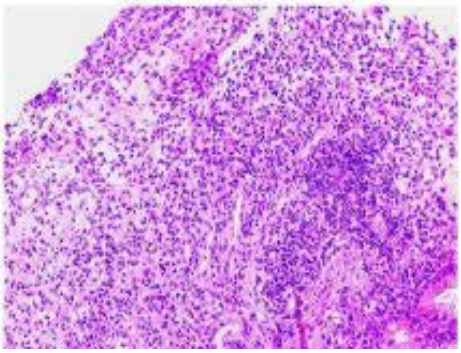

Figure 3. Lymphocytes, plasma cells and eosinophils
图 3. 淋巴细胞、浆细胞及嗜酸性粒细胞

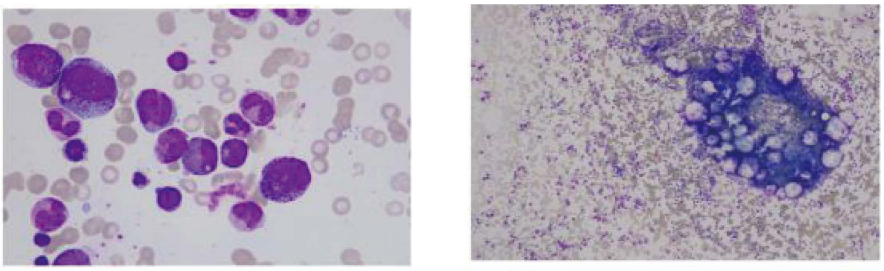

Figure 4. Bone marrow smear: leukocytosis, left shift of granulocyte nuclei, and thrombocyto
图 4. 骨髓涂片：白细胞增多，粒系核左移，血小板增多

2. 讨论

溃疡性结肠炎近些年来在总体人群发病率和患病率呈逐渐上升的趋势[1]。其发病机制受遗传易感性、肠道微生物改变、上皮屏障受损、免疫失调等多种因素的影响[2]。该病最常见的症状是腹泻和便血，根据疾病的严重程度和发病部位的不同，患者还会出现腹痛、粘液脓血便和里急后重感[3]，约三分之一的患者会出现皮肤、关节、眼睛和肝脏等一系列肠外组织病变[4]。结肠镜检查是诊断与鉴别诊断的重要手段之一，镜下可见粘膜病变呈持续性、弥漫性分布，黏膜血管纹理模糊、紊乱、消失或有脓性分泌物附着，若病情较重还可见糜烂和多发性浅溃疡[5]。早期溃疡性结肠炎组织反应是表面血流量增加，内镜下可见弥漫性颗粒状红斑和血管充血的征象。触碰黏膜容易出血，这种易碎性或接触性出血是 UC 典型的早期特征。随着炎症的进展，粘膜表面开始出现微小溃疡，导致自发出血。与克罗恩病不同的是，这些溃疡大多是局限于粘膜层和粘膜下层的浅表溃疡[6]。最近的研究表明，UC 的粘膜炎症还与免疫-非免疫细胞间复杂的相互作用有关[7] [8] [9]，患者常会伴随血小板形态、数量及功能的异常，如血小板数量增加、平均体积减小、宽度增加、分泌颗粒增多等。有研究表明，炎症性肠病患者中血小板增多的发生率高达 33% [10]，提示血小板可能在该病病程中起重要作用[11]。

血小板是由成熟的骨髓巨核细胞分泌的具有生物活性的小块胞质，是人体血液中除红细胞外数量最多的细胞成分，主要起止血作用[12]。血小板增多症在临床上分为原发性和继发性两种。原发性血小板增多症是一种慢性骨髓增殖性疾病，其特征为血小板数量显著增多(>1000 × 10^9/L)，骨髓象以原始和幼稚巨核细胞增多为主，JAK-2 基因检测呈阳性，患者出血、血栓等事件发生率较高[13]。继发性血小板增多症常继发于一些急慢性炎症、恶性肿瘤、慢性失血、脾切除术等，其中以感染最多见。主要特征是一过性的血小板增多，患者通常无症状，去除病因后血小板数量可于短期内恢复，患者出血、血栓事件发生较少[13]。

血小板生成的调控主要依赖血小板生成素(TPO)介导的负反馈机制[10]。在静息状态下，内皮细胞释放 CoX (前列环素)和 NO (一氧化氮)，它们能抑制血小板活化并且阻止血小板聚集[14]。当内皮受损后，血小板会迅速粘附于损伤部位暴露出的胶原蛋白和基底膜蛋白上，并通过其糖蛋白与胶原和胶原沉积的 vWF (血管性血友病因子)相互作用，诱导血小板活化[14]。活化的血小板释放 ADP、5-羟色胺、血栓素(TXA2)、肾上腺素等一些活性介质，并激活特定的信号通路，产生凝血级联反应，从而导致更多血小板被激活[15]。当血小板活化后胞内的一些致密颗粒、溶酶体和 α 颗粒可释放细胞因子，如组胺、前列腺素 E2 和 D2、血小板衍生生长因子、血栓素 A2 等，导致粘膜炎症[16]。P-选择素(CD62P)是 α 颗粒中一种膜糖蛋白，主要作用是促进中性粒细胞的渗出和粘附，是经典的促炎因子[17]。此外，活化血小板还分泌可溶性CD40L，这是一种与肿瘤坏死因子(TNF)家族成员同源的蛋白质，可与大多数免疫细胞表面的CD40

结合，诱导免疫活化和炎症的发生[18] [19]。活化的血小板表面还可与多种凝血因子结合，并释放纤维蛋白原，最终形成网状纤维蛋白沉积和坚实的血凝块，从而堵住血管的破口，形成血栓[20]。

3. 治疗

溃疡性结肠炎治疗目标是诱导并维持症状缓解及黏膜愈合，防治并发症，改善患者生活质量。治疗药物主要包括氨基水杨酸类、糖皮质激素、免疫抑制剂和 TNF-α 的单克隆抗体治疗。根据病情的严重程度选择合适的治疗方式是治疗是否成功的关键环节[21]。溃疡性结肠炎根据其严重程度通常分为缓解、轻度、中度或重度。轻中度疾病的一线治疗是氨基水杨酸类药物，对此类药物无反应或未达到缓解的患者可使用糖皮质激素治疗；中度至重度结肠炎患者和激素依赖型患者则需加用硫嘌呤或生物药物；急性重度溃疡性结肠炎患者应静脉注射糖皮质激素，对于应用激素无效的患者，可以尝试环孢素或英夫利昔单抗治疗。对于一些不可控制的出血、穿孔、结直肠癌等复杂性疾病则需手术[3] [22]。

继发性血小板增多症以治疗原发病和祛除病因为主，一般不需要针对性治疗，在血小板数量大于 1000×10^9/L 时，可使用羟基脲、干扰素等降低血小板数量。羟基脲是一种骨髓增生抑制剂，其可选择性阻碍 DNA 合成，抑制巨核细胞增生分化，减少血小板数量[23]，是目前治疗血小板增多症最常用的一线药物。Cortelazzo 等人在一项前瞻性研究中发现，接受羟基脲治疗的高危疾病患者的血栓事件明显少于未接受骨髓抑制治疗的患者[24]。α 干扰素(IFN)是一种蛋白质因子生物制剂，具有抑制细胞增殖、抗病毒、调节免疫及抗肿瘤等作用，目前已广泛应用于治疗血小板增多症。有大量研究表明，羟基脲联合干扰素治疗血小板增多症可提高疗效，延长药效持续时间，减少不良反应的发生，具有更高的安全性。本例患者于外院常规美沙拉嗪抗炎等治疗效果不明显，于我院行骨髓穿刺活检后明确诊断为溃疡性结肠炎合并继发性血小板增多症，给予美沙拉嗪抗炎治疗的同时联合羟基脲及干扰素降血小板数量，并辅以益生菌调节胃肠功能、抗生素抗感染、补蛋白及充营养素后症状明显好转，1 月后复查肠镜提示溃疡性结肠炎处于缓解期，血小板数量明显减少，随访 6 个月病情稳定。

4. 总结

越来越多的证据表明，血小板在肠道炎症过程中发挥重要作用，即使在炎症的非活动期，血小板的这种过度活动也可能对炎症反应产生强化和加重的影响[25]。所以在临床诊治过程中，我们一定要重视溃疡性结肠炎引起血小板增多这一情况，正确区分原发性血小板增多症和继发性血小板增多症，避免误诊，而且在治疗原发病的同时注意控制血小板的数量，以达到更好的治疗效果。

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