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疑难病例

误诊为“先天性巨结肠”的 *ATCG2* 基因突变相关内脏肌病 1 例

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摘要: **目的** 探讨一例内脏肌病患者的诊断、鉴别诊断和并发症的治疗。**方法** 详细收集患者病史、体格检查和辅助检查等临床资料,复核手术病理,送检全外显子基因测序,并通过一代测序完善突变位点的家系验证。**结果** 患者为青年女性,幼儿期起病,临床表现为反复不全肠梗阻,被诊断为“先天性巨结肠”,多次行胃肠切除手术。术后肠梗阻症状可短暂缓解。但未次手术后逐渐出现严重腹泻、黏液血便及营养不良。评估考虑患者慢性假性肠梗阻继发小肠细菌过度生长及肠道机会性感染,予抗感染、肠内要素饮食等对症治疗后好转。进一步完善病理会诊及全外显子基因测序,明确诊断为 *ATCG2* R148L 基因突变相关内脏肌病。**结论** 对起病早、常规治疗反应差的慢性假性肠梗阻患者可完善基因检测。遗传性内脏肌病患者易合并肠道机会性感染,应关注并发症的防治,避免不必要的手术。

关键词: 慢性假性肠梗阻;肠道机会性感染;内脏肌病;先天性巨结肠

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A case of visceral myopathy with *ATCG2* gene mutation misdiagnosed as Hirschsprung disease

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Abstract: Objective To discuss the clinical features, differential diagnosis and complication treatment of a patient with genetic visceral myopathy. **Methods** Medical history, physical examination and laboratory results of the patient were collected in detail. The pathology of previous surgery was reviewed. The patient's peripheral blood DNA was extracted and submitted for whole-exome sequencing. Subsequent Sanger sequencing was used to complete the pedigree verification of the mutation site. **Results** The patient was a young female presented with repeated incomplete intestinal obstruction since early childhood. She used to be misdiagnosed as Hirschsprung's disease for a long period and underwent multiple gastrointestinal segment resections. Her intestinal obstruction symptoms were temporarily relieved by surgeries, but severe diarrhea, mucus and bloody stools and malnutrition gradually occurred after the last operation. The patient had bacterial overgrowth in small intestinal tract and followed by intestinal opportunistic infections secondary to chronic intestinal pseudo-obstruction. The symptoms improved after anti-infection

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and enteral element diet treatment. Further pathological consultation and whole-exome gene sequencing confirmed the diagnosis of visceral myopathy related to *ATCG2* R148L mutation. **Conclusions** Patients with early onset of chronic intestinal pseudo-obstruction and have poor response to conventional treatment are recommended to perform genetic test. The patients with hereditary visceral myopathy are susceptible to opportunistic intestinal infection. Attentions should also be paid to the prevention and treatment of complications to avoid unnecessary surgery.

Key words: chronic intestinal pseudo-obstruction; intestinal opportunistic infections; visceral myopathy; Hirschsprung disease

1 病例

1.1 病史

患者,女性,25岁,因“腹胀、呕吐20余年,腹泻1年余”收入北京协和医院消化内科。患者幼儿期开始间断餐后腹胀、大便干结,调整饮食、服用健胃消食片可好转。2005年起腹胀加重,常餐后1h呕吐胃内容物,每天排1~2次成形软便。外院查胃镜示“幽门糜烂、狭窄”。行内镜下幽门球囊扩张2次,呕吐好转,但仍有腹胀、腹部膨隆。2013年12月消化道造影示“胃窦远端狭窄,扩张度差,结肠传输缓慢”。立位腹平片见“肠管胀气明显伴多发液气平”。诊断“先天性巨结肠”可能,行“横结肠切除+阑尾切除术”。术后症状缓解欠佳。2014年6月腹胀加重,腹部CT示“空、回肠肠壁弥漫性炎性增厚,回肠下段管腔狭窄致不全性梗阻,回肠中上段及空肠下段继发性扩张;幽门肥厚狭窄”。行“远端胃切除+胃-十二指肠端侧吻合术,结肠次全切除+回肠-乙状结肠侧侧吻合术”。病理:(幽门)平滑肌细胞瘤样增生;(结肠、回肠)黏膜慢性炎伴糜烂,肌层平滑肌增生,局部肌间神经节细胞缺如,符合巨结肠。术后腹胀好转,排成形软便2~3次/d。但仍每年发作3~4次不全肠梗阻,对症治疗3d左右可好转。2021年6月患者进食不当后持续腹痛,排气排便停止5d。外院诊断肠梗阻,切除剩余结肠及部分小肠,行小肠-直肠残端吻合术。术后病理:(结肠和部分小肠)慢性肠炎伴管腔扩张,肌层神经节细胞少,符合先天性巨结肠。术后腹泻糊状便,10余次/d,每次50~100mL,无脓血。2021年8月复查结肠镜:深入小肠约200cm,所见回肠全程扩张,数处成角明显,伴口侧肠内容物潴留,小肠蠕动缓慢甚至消失,黏膜水肿,吸引或镜身触及易出血。口服益生菌,仍有腹泻、乏力、纳差。2022年3月再发腹痛,肠镜示小肠极度扩张、多发溃疡,吻合口溃疡。口服

美沙拉秦无改善。2022年8月患者20余天未排便,再次肠梗阻,麻醉下扩肛、取出潴留粪块、温肥皂水灌肠等治疗后好转。2022年10月患者再次间断腹泻,每天10余次黑褐色稀便,每次约100mL,偶带脓血,伴头晕、心悸。查血红蛋白44g/L,多次输血及对症治疗仅部分改善。2023年2月进食不当后腹泻加重至水样便20次/d,伴乏力。查血红蛋白约40g/L。腹部CT示小肠明显扩张。肠镜见小肠多发糜烂。输血及对症诊疗效果欠佳,为进一步诊治入院。个人史:患者婴儿期无吐奶或腹部膨隆不适,生长发育情况与同龄人相近。家族史:父亲患幽门肥厚、结肠扩张、小肠扩张,曾多次因肠梗阻行手术治疗。2021年肠梗阻手术后去世。2个姑姑、1个姐姐无消化系统疾病。入室查体:脉搏76次/min,血压110/52mmHg(1mmHg=0.133kPa),体质指数15.6kg/m²。营养不良,贫血貌,双肺呼吸音清,心律齐,腹部多处手术疤痕,舟状腹,腹软,无压痛,全腹叩诊鼓音,肠鸣音1次/min,双下肢无水肿。

1.2 诊疗经过

入院完善血常规:白细胞 $5.02 \times 10^9/L$,血红蛋白79g/L,平均红细胞体积110.4fL,平均红细胞血红蛋白浓度32.9pg,血小板 $610 \times 10^9/L$,网织红细胞%7.24%;粪便常规+潜血:白细胞0/HPF,红细胞0/HPF,潜血阳性(+);血生化:白蛋白36g/L,谷丙转氨酶11U/L,肌酐48 $\mu\text{mol/L}$,钾4.5mmol/L;血清铁31 $\mu\text{g/dL}$,铁蛋白104ng/mL,维生素B₁₂138pg/mL。超敏C反应蛋白0.94mg/L,血沉9mm/h。粪便细菌培养、真菌培养、抗酸染色阴性;难辨梭菌毒素阳性;甲烷和氢气呼气试验阳性,提示小肠细菌过度生长(small intestine bacteria overgrowth, SIBO)。肠道彩超:吻合口处小肠肠壁增厚,较厚处0.6cm,回声减低,其近心端小肠肠腔宽约4.2cm,小肠绒毛结构消失,肠壁稍增厚,较厚处厚约0.4cm,回声减低;腹腔多发小肠肠腔扩张,

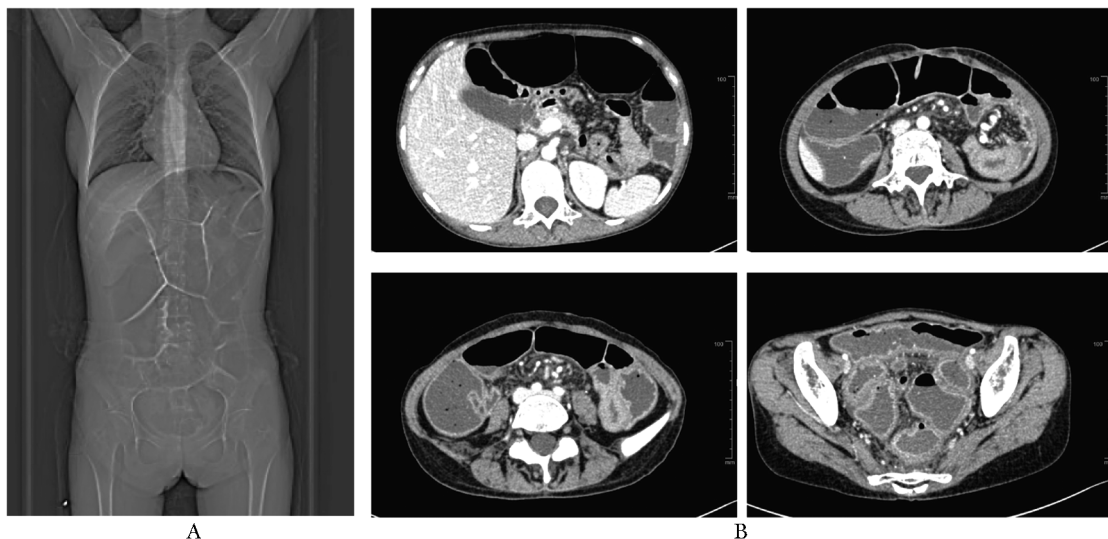
较宽处 3.6 cm; 检查中可见少许蠕动。腹盆 CT: 腹盆腔部分小肠肠壁增厚、肠腔扩张积液伴多发液平, 考虑小肠梗阻或不全梗阻(图 1)。肛门直肠测压: 直肠肛门抑制反射不存在。

结肠镜: 循腔进镜 20 cm, 可见大量血便残留。所见小肠黏膜绒毛消失, 可见多发条状溃疡和血泡样伪膜形成(图 2)。考虑“慢性假性肠梗阻、难辨梭菌感染、小肠细菌过度生长”。予全安素饮食, 口服万古霉素 125 mg qid、甲硝唑 0.4 g tid、利福昔明 0.2 g qid, 补充益生菌、铁剂、甲钴胺、叶酸等治疗。患者一般情况好转, 逐渐恢复至 1 次软便/d。

为明确病因, 取外院手术标本病理会诊。2014 年 6 月手术标本:(远端胃)胃壁部分内肌层增

厚, 扭曲紊乱, 肌纤维变性, 可见神经节及节细胞;(小肠及结肠)小肠灶性黏膜表面上皮脱失, 近表面隐窝损伤破坏, 部分肌层肌纤维栅栏状排列, 未见明显神经节及节细胞减少, 黏膜及肠壁血管扩张充血, 偶见肠系膜血管壁厚薄不均, 淋巴结显慢性炎。2021 年 6 月手术标本:(结肠+部分小肠)小肠壁部分肌间神经节稀疏, 神经节内节细胞数量未见明显减少, 部分肌层肌纤维栅栏状排列。上述病理形态倾向于胃肠道神经及肌组织发育异常。

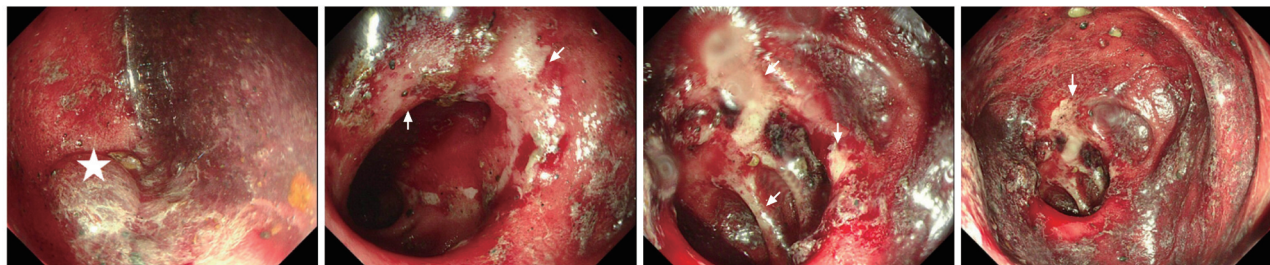
进一步送检全外显子测序, 结果回报 *ATCG2* 基因杂合突变 NM_001615.3:c.443G>T (p.Arg148Leu), 编码区第 443 位核苷酸由鸟嘌呤突变为胸腺嘧啶, 致蛋白质第 148 位精氨酸错义突变为亮氨酸。进一步完



A. the CT topogram showed dilated small intestinal loops with air accumulation; B. axial portal phase enhanced CT showed thickening wall and dilation with air-fluid levels of partial small intestine.

图 1 患者腹腔及盆腔增强 CT

Fig 1 Abdominal and pelvic enhanced CT scan of the patient



The small intestinal villi disappeared with multiple striped ulcers (arrows) and blood blister-like pseudomembrane (asterisk).

图 2 患者结肠镜图像

Fig 2 Colonoscopic images of the patient

善家系基因检测,明确患者该突变来自于父亲遗传。符合 *ATCG2* 基因突变相关内脏肌病。本研究通过北京协和医院伦理委员会批准(批准号: I-23PJ525),受试者充分知情同意,并签署同意书。

2 讨论

患者反复消化道梗阻,影像可见肠道扩张,但无机械性梗阻证据,符合慢性假性肠梗阻(chronic intestinal pseudo-obstruction, CIPO)^[1]。消化道运动依赖于肠神经、Cajal 间质细胞和平滑肌功能的协调统一,任何环节障碍均可导致 CIPO^[2-3]。

患者起病年龄小、消化道受累广泛,结合家族史,需考虑先天发育异常。先天性巨结肠(Hirschsprung's disease, HD)以肠壁肌间神经节细胞缺如为重要特征,常累及直肠和乙状结肠,全结肠、小肠受累非常罕见^[4-5]。患者病理未见明显神经节细胞缺如,不支持 HD。全外显子测序明确其携带 *ATCG2* R148L 杂合突变。*ATCG2* 编码 gamma 平滑肌肌动蛋白,是肠道、泌

尿道、子宫平滑肌的主要肌动蛋白亚型,其突变引起 *ATCG2* 蛋白功能障碍是肌源性 CIPO,即内脏肌病的重要致病原因^[6]。*ATCG2* R148L 突变曾在一澳大利亚 CIPO 家系中被报道^[7]。

内脏肌病消化道长节段受累,其所致 CIPO 的管理包括 5 个重要维度:患者教育、保证摄入、协调胃肠道运动、治疗并发症、避免非必要的手术^[8-9]。推荐少量多次经口进食,避免高脂、易发酵食物,必要时可泵入肠内营养制剂。重度梗阻、营养不良者需肠外营养支持。急性梗阻时应以胃肠减压、对症支持为主,避免非必要的手术。CIPO 易合并肠道感染,本例患者存在 SIBO 同时合并难辨梭菌感染,使用利福昔明、万古霉素、甲硝唑规范治疗^[10-12]后,患者腹泻、便血明显好转,生活质量改善。

在 CIPO 诊治中应重视病因诊断,在形态、功能评价基础上酌情行病理和基因检测。遵从 CIPO 管理模式,保证摄入充足、减少急性发作,积极预防和处理并发症,改善患者生活质量和远期预后。

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