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·综述·

结直肠无蒂锯齿状病变癌变的内镜及通路改变

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【提要】 结直肠癌是中国发病率居高的消化系统恶性肿瘤,15%~30%的散发结直肠癌来源于锯齿状病变癌变途径。锯齿状病变内镜下表现、分子信号通路改变、病理改变、自然病程等与经典“腺瘤-癌”途径不同,特别是无蒂锯齿状病变,由于内镜下发现率低,病灶边缘不清导致不完全切除,是间期癌的重要来源。因此,认识无蒂锯齿状病变非常重要。本文就无蒂锯齿状病变分类、内镜下 pit pattern 分型、分子改变特征作一综述。

【关键词】 结直肠肿瘤; 癌前状态; 无蒂锯齿状病变; pit pattern; 信号通路

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Endoscopic and pathways changes in carcinogenesis of colorectal sessile serrated lesions

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随着生活方式及饮食结构的改变,结直肠癌发病率呈上升趋势,现已成为我国发病率居首的消化系统恶性肿瘤^[1-4]。15%~30%的散发结直肠癌来源于锯齿状病变癌变途径(serrated pathway, SP),无蒂锯齿状病变(sessile serrated lesions, SSLs)是间期癌的重要来源,因此提高对SSLs的认识非常重要^[5]。结肠镜检查是整个筛查流程的中心环节,应用放大内镜、色素染色等技术,结合工藤进英教授提出的观察腺管开口形态及排列的pit pattern分型,可以有效提高锯齿状病变的检出率,并判断病变进展程度,有利于治疗方案确定^[6-9]。结直肠正常黏膜-癌前病变-癌的转变过程,伴随着一系列局部环境及分子信号改变,从而导致组织形态学的变化,随着技术发展,鉴定出SP的关键分子及信号通路改变,同时也明确肠道菌群及微环境改变在SSLs形成及SP中发挥重要作用^[10-16]。

一、锯齿状病变的分类

世界卫生组织2019年第5版指南推荐将锯齿状病变分为3类:增生性息肉(hyperplastic polyps, HPs)、SSLs、传统锯齿状腺瘤(traditional serrated adenomas, TSAs)^[17]。本版指

南推荐用SSLs替代之前的无蒂锯齿状腺瘤或息肉,同时强调单个结构异常的隐窝即可诊断为SSLs,该诊断标准提高了病理专家之间诊断的一致性及诊断灵敏度^[18-19]。由于既往各版本的诊断标准、命名规范以及内镜医师检出率的变化,锯齿状病变的患病率难以确定。在筛查人群中,锯齿状病变占结肠镜检出所有息肉的11%~53%,HPs是最常见的,占有锯齿状病变的80%~90%,SSLs占15%~20%,TSAs最不常见,占1%~6%^[20]。HPs的一个亚类——微泡型增生性息肉,被认为是SSLs的前体病变,SSLs及TSAs有恶性潜能^[21]。

二、SSLs的大体及pit pattern形态

在肠镜检查、病理评估中很容易忽视SSLs,这是间期癌的主要来源,也是结直肠癌筛查失败的原因之一。内镜设备、附件及技术的发展提高了SSLs内镜的发现、诊断、治疗效果。临床上多以普通白光观察为主,适当分多次变换窄带光成像(narrow band imaging, NBI)、蓝光成像(blue laser imaging, BLI)、联动成像(linked color imaging, LCI)观察,对锯齿状病变的检出更具优势,放大和窄带光成像

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(magnifying endoscopy with narrow-band imaging, ME-NBI) 观察后,靛胭脂白光下或放大观察、结晶紫染色放大观察,对锯齿状病变的边界、性质等可以作出较准确的判断。如怀疑有深浸润时需进一步进行超声内镜检查或影像学检查,综合制定治疗方案^[22-23]。随着超广角内镜、内镜前端附件(如ENDOCUFF VISION)、无创喷洒管、LCI、人工智能辅助识别技术等的应用,虽然各自有其限制,但总体上利于SSLs的检出。

SSLs多位于右半结肠,直径多>5 mm,表面常附黏液帽,形态不规则,边界不清。当病灶为浅表隆起或浅表凹陷时,白光下准确识别病灶有一定难度,应用LCI模式或靛胭脂染色可提高检出率^[24-25]。靛胭脂染色能强化病灶边界、表面凹凸结构,突出病灶的立体感,结合放大观察也能判断pit pattern。应用NBI、ME-NBI,根据病灶的微血管形态、表面结构、背景黏膜颜色,可以预测病灶类型及浸润深度,病灶的日本窄带光成像技术专家小组(Japan NBI expert team, JNET)分型为2B型或3型时,进行结晶紫染色放大观察进一步进行pit pattern诊断^[26-28]。可以综合应用高清白光内镜、图像增强技术(NBI、LCI、BLI等)、色素染色内镜等技术对pit pattern进行判断,对判断病灶性质及浸润程度至关重要。

SSLs内镜下pit pattern分型呈Ⅱ型星芒状、Ⅱ-O型, JNET分型多为1~2A型^[29]。当病变进展伴异型增生时,进展为癌的时间明显缩短,在SSLs伴异型增生到癌变过程中,内镜下可发现带蒂、亚蒂,双隆起,中央凹陷,表面发红等改变,pit pattern多呈Ⅲ、Ⅳ型, JNET分型多为2B型;当黏膜内出现癌腺管后,内镜下进一步发现紧满感、表面粗糙、皱襞集中的改变,pit pattern排列紊乱,并且变得不规则(V₁型pit, I: irregular), JNET分型多为3型,从病理组织像可见表层腺管的异常构造^[30]。随着癌组织向黏膜下深部浸润,黏膜层的构造破坏明显,同时伴有明显的间质反应,可以看到无构造或是接近无构造的pit pattern图像(V₂型pit, N: non-structure),这种表现意味着癌向黏膜下层浸润生长,通过SP产生的晚期癌约2/3的病灶会失去锯齿状组织学特征^[31]。

组织病理学是诊断早期结直肠癌及癌前病变的金标准,图像增强技术以及激光共聚焦内镜,Endo-Cytoscopy内镜系统,不需要活检就能模拟获取组织病理图像,甚至观察到细胞水平,这对实时判断病理性质有价值^[32]。

三、SSLs癌变主要分子信号通路改变

1. 结直肠癌分子亚型共识(the consensus molecular subtypes of colorectal cancer, CMS)分类与SP: 15%~30%散发结直肠癌来源于SP,数量仅次于“腺瘤-癌”途径。SP来源的结直肠癌组织形态上经历了正常黏膜-HPs-SSLs、TSAs-癌的转化,基因的沉默可以通过基因序列改变(突变、染色质畸变等)和表观遗传修饰(DNA甲基化、组蛋白翻译后修饰、miRNA等)来实现。得益于高通量测序、转录组学、生物信息学的发展,2015年在整合优化了之前数种结直肠

癌分类的基础上,提出了CMS,把结直肠癌分为4类,与SP关联紧密的是CMS1、CMS4型^[33-40]。CMS1型约占结直肠癌的14%,即微卫星不稳定强免疫反应型,以BRAF突变、超突变、微卫星不稳定、强免疫激活浸润为特点,预后相对较好。CMS4型,即间充质型,约占结直肠癌的23%,以转化生长因子- β (TGF- β)活化、基质侵袭和血管生成成为特点,预后差^[41]。SSLs癌变涉及的主要分子信号通路改变有BRAF^{V600E}突变、KRAS突变、微卫星不稳定、CpG岛甲基化表型(CpG island methylator phenotype, CIMP)。

2. DNA甲基化与CIMP: DNA甲基化是调节基因表达的表观遗传修饰之一。在人类, DNA甲基化修饰位于鸟嘌呤之前的胞嘧啶残基处,称为CpG二核苷酸,人类基因组中存在富含CpG序列的CpG岛,通常在正常健康细胞中未甲基化,40%~60%的肿瘤抑制基因的启动子区域存在CpG岛,CG含量>50%^[42-43]。结肠肿瘤呈整体DNA低甲基化,局部高甲基化^[44-45]。DNA高甲基化可以通过对启动子和非编码DNA元件(例如增强子)的影响使肿瘤抑制基因沉默。整体DNA低甲基化,通过诱导染色体不稳定性、印记的整体丢失和超级增强子激活来影响结直肠癌的发展。CIMP可分为低(CIMP-L)、高(CIMP-H)或阴性(CIMP-0),具体取决于位于肿瘤抑制基因启动子区域附近的CpG岛中同时发生的甲基化程度^[46-47]。较为认可的定义CIMP表型的有两类基因组合。第一类由Toyota提出,包含P16、hMLH1、MINT1、MINT2和MINT31;第二类由Weisenberger提出,包含CACNA1G、IGF2、NEUROG1、RUNX3和SOCS1^[48-49]。现在通过全基因组甲基化分析来评估CIMP,为结肠癌分类提供了新方向。

SSLs来源的结直肠癌中,多位于近端结肠、女性、具有黏液性组织学特征。从微泡型增生性息肉到SSLs,具有典型的BRAF^{V600E}突变,激活了MAPK信号通路,因CIMP-H而沉默多种抑癌基因,当发生异型增生及癌变时,激活WNT/ β -catenin信号通路,或WNT信号通路相关基因如SFRP家族(CDX2、MCC蛋白)、也可激活P53信号通路(IGFBP7蛋白)、细胞周期控制信号通路(CDKN2A蛋白)等^[50-52]。当DNA错配修复家族蛋白(MLH1)发生超甲基化或突变后,形成微卫星不稳定表型,发展为癌的时间明显缩短。若MLH1没有发生超甲基化,则可联合WNT通路、TGF- β 、上皮-间质转化等通路,形成微卫星稳定型结直肠癌,这类结直肠癌更多以含BRAF突变的TSAs作为前体,形成CMS4型结直肠癌(高水平体细胞拷贝数变化、染色体不稳定、CIMP-L、微卫星稳定),预后差^[53-54]。不同的是,大部分TSAs来源的结直肠癌含有KRAS突变,携带RSPO融合转录物,且呈CIMP-L状态。

3. DNA错配修复系统与微卫星不稳定: 微卫星不稳定是指由于DNA错配修复系统(mismatch repair, MMR)缺陷导致的超突变表型^[55]。林奇综合征的微卫星不稳定继发于DNA错配修复系统蛋白种系突变,而DNA错配修复系统的表观遗传沉默更常见于散发性结直肠癌。微卫星不稳定与

肿瘤的异质性、肿瘤新抗原形成、免疫治疗、预后密切相关。聚合酶链反应(polymerase chain reaction, PCR)和免疫组织化学(immunohistochemistry, IHC)方法常用于临床微卫星不稳定测试^[56-57]。PCR 分析用于检测微卫星重复序列的不稳定性,而 IHC 用于检测一种或多种 DNA 错配修复系统蛋白(MLH1、MSH2、MSH6 和 PMS2)的表达缺失。根据 Bethesda 共识指南定义的标准微卫星标记组数量确定微卫星不稳定状态,分为高度微卫星不稳定、低度微卫星不稳定、微卫星稳定,但这种方法也有其局限性^[58-59]。

杯状细胞型增生性息肉向 TSAs 的发展过程与 KRAS 突变及 CIMP-L 相关,由其发展来的结直肠癌大多呈微卫星稳定表型^[60]。微泡型增生性息肉向 SSLs 的发展过程常见 BRAF^{V600E} 突变及 CIMP-H 表型,当出现 SSLs 伴异型增生时,则多出现 MLH1 超甲基化和高度微卫星不稳定^[61-62]。CMS1 型结直肠癌由于 BRAF^{V600E} 突变与 MLH1 基因启动子区域高甲基,导致 MLH1 和 PMS2 同时表达缺失, DNA 突变累积(尤其是移码突变),并表达多种突变形式的蛋白,这些蛋白功能缺失,但保留了免疫原性,是肿瘤源性的新抗原,诱发强免疫激活浸润,如 TIL、IFN- γ 相关基因的表达、WNT/ β -catenin 信号通路紊乱等。结直肠癌能表达大量的新抗原,这是免疫治疗的靶点,如 PD-1。CMS1 型结直肠癌对氟嘧啶单药辅助化疗无效,甚至可能有害^[63]。微卫星不稳定是驱动产生肿瘤内异质性(intratumor heterogeneity, ITH)最重要因素之一,ITH 在空间上表现为肿瘤细胞之间不同的遗传改变和表型,在时间上表现为自然肿瘤进展和治疗干预期间亚克隆的变化^[64-66]。因此面对高度异质性的结直肠癌,进一步发展现有的免疫治疗方法如免疫检查点阻断,开发早筛及预后标志物如循环肿瘤 DNA、循环肿瘤细胞,做到结合患者实时状态,给予精准治疗和预后判断,是临床需要解决的问题^[67]。

4. 突变表型与相关通路: SSLs 癌变途径与 WNT、RAS-MAPK、PI3K、TGF- β 、TP53 和 DNA 错配修复信号通路都有关联, BRAF^{V600E} 是主要驱动突变^[68]。

在微泡型增生性息肉向 SSLs 及结直肠癌的发展过程中, BRAF^{V600E} 突变可能是起始驱动因素,导致组成型 MAPK 通路的信号传导, KRAS 也通过该通路发出信号,导致细胞增殖、存活和细胞凋亡的抑制^[69]。 BRAF^{V600E} 突变能诱导 IGFBP7 的合成和分泌,联合 P16^{INK4a}、P53 诱导衰老,抵抗致癌突变^[70]。当 IGFBP7、P16^{INK4a} 被甲基化沉默后,打破平衡,无序扩增,在 CIMP-H 及高度微卫星不稳定的状态下,主要累及 WNT、RAS-MAPK 信号通路向 CMS1 型结直肠癌发展。在 CIMP-L 及低度微卫星不稳定或微卫星稳定的状态下,主要累及 P53、PI3K、TGF- β 信号通路,向 CMS4 型结直肠癌发展。近期通过结肠类器官及基因编辑技术明确, BRAF^{V600E} 突变联合超甲基化表型,可以激活 WNT 通路,明显缩短锯齿状病变形成时间^[71]。与传统“腺瘤-癌”途径通过 APC 截断突变激活 WNT 通路不同, SP 主要通过 APC 错义突变、RNF43 突变、SFRP4、MCC、AXIN2 的甲基化,激活 WNT

通路^[72-75]。

在 SP 中 BRAF 与 KRAS 突变一般互斥, BRAF 突变比 KRAS 突变诱导更高水平的基因甲基化,更易形成 CIMP-H、高度微卫星不稳定表型^[76]。在 BRAF 突变条件下,通过 MAFK 招募阻遏复合物介导 CIMP 基因启动子及 MLH1 沉默,在 KRAS 突变条件下,通过 ZNF304 招募阻遏复合物介导,这说明 SP 路径中 BRAF 与 KRAS 选择性地招募不同阻遏物复合物结合到 CIMP 基因启动子,起到沉默基因的作用^[77]。

突变特征、场癌化、表观遗传漂移等概念的提出,再次提示癌症是一个动态过程,在形态正常的组织中也有基因(如碱基替代、插入、缺失、重排、拷贝数异常等)及表观遗传(如 DNA 甲基化、非编码 RNA 异常)改变,这可能是原始病灶特征,并且随着年龄、微环境的改变,在遗传与表观遗传的改变累积到相当程度后,则发生形态学改变,逐步进展为癌^[78-79]。SSLs 来源的结直肠癌的具有独特的组织学表现,通过对大量单个隐窝的测序,发现在形态正常的肠上皮中也存在肿瘤性分子改变,在癌症进化过程中赋予选择性优势的突变为驱动突变,推测结直肠癌发展的最早阶段是许多带有驱动突变的隐窝,而病变的发展伴随着突变负荷增加^[80-82]。这些突变特征、突变负荷的鉴定揭示每位患者肿瘤生物学特征,为个性化精准医疗提供意见。

综上,结直肠的组织胚胎来源不同,肠道微生物与微环境因解剖位置而差异显著,这对 SP 来源的结直肠癌更精确的分类及病因发现增加困难。随着类器官培养、基因编辑、肠道菌群实时鉴定等技术的发展,提供了更确信的纵向研究证据,综合评估将对 SP 来源的结直肠癌的分型、研发早期识别标志物、临床治疗、预后监控等产生积极的指导作用。

利益冲突 所有作者声明不存在利益冲突

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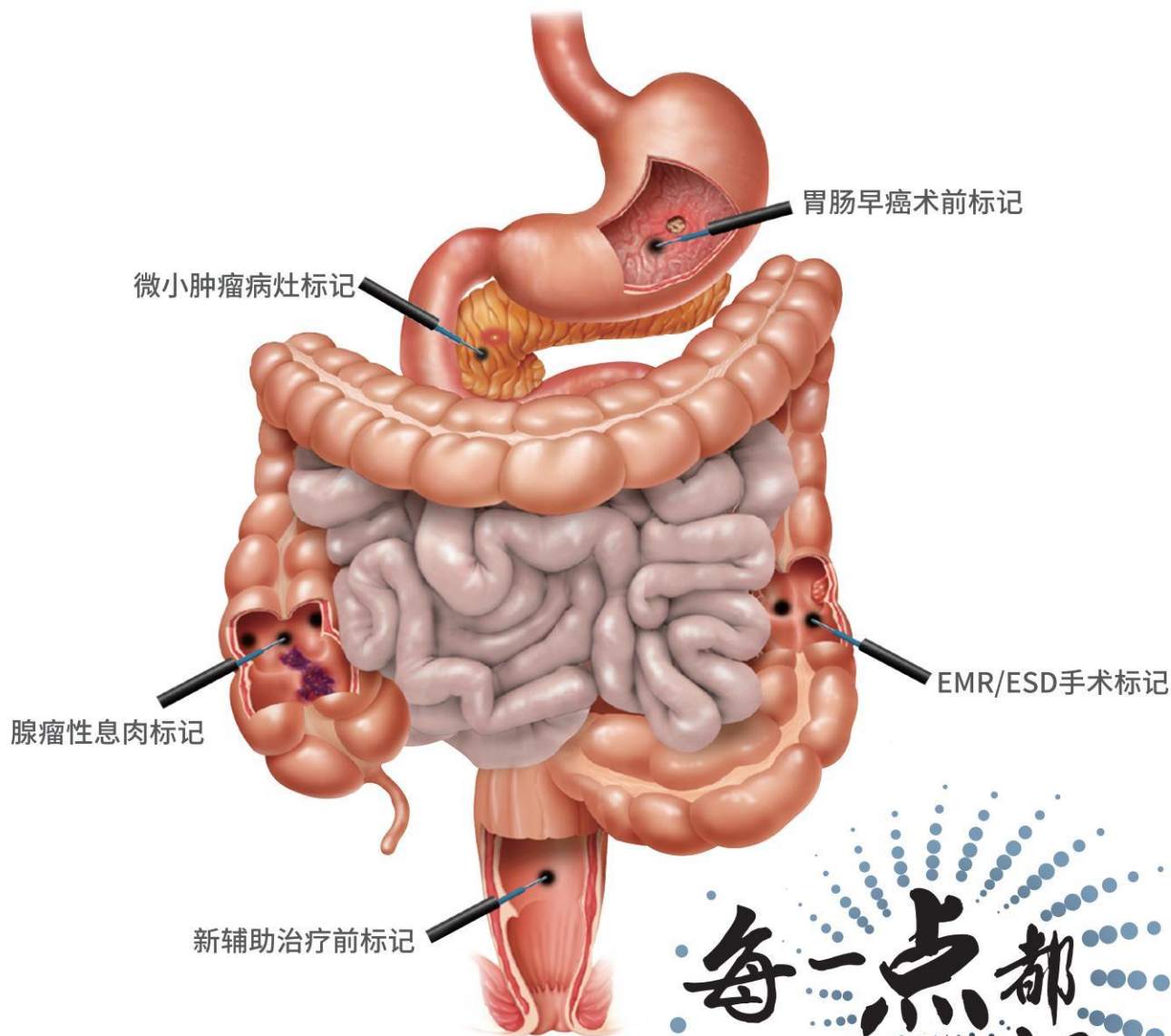


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