世界华人消化杂志 2013年4月28日; 21(12): 1090-1095
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

胃增生性息肉的研究进展

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■背景资料
胃增生性息肉(gastric hyperplastic polyps, GHP)是胃息肉中最常见的息肉样病变之一, 目前已证实其具有癌变潜能. GHP发病机制不明, 至今仍未发现能特征性提示GHP将发生恶性转变的标志物.

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收稿日期: 2013-01-29 修回日期: 2013-03-04
接受日期: 2013-04-12 在线出版日期: 2013-04-28

An overview of current research of gastric hyperplastic polyps

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Received: 2013-01-29 Revised: 2013-03-04
Accepted: 2013-04-12 Published online: 2013-04-28

Abstract
Gastric hyperplastic polyp (GHP) is one of the most common polypoid lesions of the stomach and has the potential of malignant transformation. This article gives a review of recent progress in research of GHP in terms of clinical and pathological factors, pathogenesis, relation with atypical hyperplasia and canceration, molecular biology and mucin expression.

Key Words: Gastric hyperplastic polyps; Pathogenesis; Molecular biology; Mucin phenotype

Song MY, Li J, Jiao YF. An overview of current research of gastric hyperplastic polyps. Shijie Huaren Xiaohua Zazhi 2013; 21(12): 1090-1095 URL: http://www.wjgnet.com/1009-3079/21/1090.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i12.1090

摘要
胃增生性息肉(gastric hyperplastic polyps, GHP)是胃息肉中最常见的息肉样病变之一, 目前已证实其具有癌变潜能. 本文主要从GHP的临床病理学因素、发病机制、GHP与不典型增生和癌变的关系、GHP的分子生物学研究和粘蛋白的表达等方面, 对GHP研究进展作一综述.

关键词: 胃增生性息肉; 发病机制; 分子生物学; 粘蛋白表型

核心提示: 胃增生性息肉(gastric hyperplastic polyps, GHP)通常被认为是一种良性病变, 但是目前越来越多的报道证实其具有癌变潜能. 有些研究结果证实GHP的癌变过程为: GHP→不典型增生→局灶癌变. 近年来, 对GHP中的粘蛋白表达的研究发现粘蛋白可能是在恶性肿瘤的早期阶段的检测、治疗及提示肿瘤预后的良好标志物. 研究GHP粘蛋白的表达情况可能是将来研究的重点内容. 本文从发病机制、分子生物学、粘蛋白的表达等方面对GHP研究进展进行概述.

宋美玥, 李娟, 焦宇飞. 胃增生性息肉的研究进展. 世界华人消化杂志 2013; 21(12): 1090-1095 URL: http://www.wjgnet.com/1009-3079/21/1090.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i12.1090

0 引言
胃增生性息肉(gastric hyperplastic polyps, GHP)是胃息肉的主要类型[1-3], 约占所有胃上皮息肉的70%-90%[2-6], 在胃窦部多见[7]. GHP通常被认为是一种良性病变, 但是越来越多的实验已证实其具有癌变潜能[8-12].

1 GHP的临床病理学因素
GHP患者年龄一般为20-88岁. 虽然大多数研究指出, 女性发病率略高, 但也有报道显示男性略多发. 患者可无症状, 通常在胃肠道内镜检查时发现息肉[13-16]. GHP可发生于胃组织的任何部位(贲门、胃体、胃底、胃窦等), 但较常见于胃窦部[7]. GHP大小从几毫米到几厘米不等, 大多数GHP的最大径是1 cm, 最大的GHP可达12 cm[17].

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GHP患者中, 20%为多发性GHP, 通常这部分患者同时患有自身免疫性胃炎[13].

2 病理学表现

大部分GHP是小的广基性息肉, 大的GHP通常可有蒂或有亚蒂. GHP的形态学特点是胃小凹上皮细胞增生, 腺体扭曲伸长, 平滑肌细胞增生以及间质水肿并伴有炎细胞浸润[18].

3 鉴别诊断

GHP与胃Peutz-Jeghers息肉在组织学上非常相似. 胃Peutz-Jeghers息肉组织病理学特点是平滑肌广泛增生形成树枝状形态, GHP的平滑肌虽然也增生, 但是并不形成如此广泛的增生. 而且, 胃Peutz-Jeghers息肉的间质中通常无炎症细胞浸润. 此外, 胃Peutz-Jeghers息肉非常罕见[19]. 胃Peutz-Jeghers息肉患者特征性的临床表现为在面部、口唇周围、颊黏膜、指和趾以及手掌和足底部皮肤等处发生色素斑. 严重者可同时出现腹痛、腹泻、黏液便、便血、便秘、呕血等消化系症状[20].

4 发病机制

GHP发病机制目前尚不清楚[21-25], 研究表明, GHP是一种修复再生性的病变. 据报道24.2%的患者随着胃黏膜损伤的愈合, 增生的小凹上皮组织会逐渐消失, 其余将发展为GHP[21].

4.1 幽门螺杆菌与GHP发生的关系 GHP的发生与各种慢性胃炎具有很大的相关性, 特别是由幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染引起的胃炎和自身免疫性胃炎[13,22]. 一些研究表明, GHP与*H. pylori*的感染密切相关[23]. Ohkusa等研究表明根除*H. pylori*能够使一定数量的GHP消失或减退[16,22-24]. 在Saccá等[16]的研究中, 虽然70%的患者*H. pylori*根除后GHP消失或减退, 但仍有部分患者*H. pylori*被根除后, GHP依然存在[16]. 还有一部分*H. pylori*检测阳性的患者未查见GHP的发生, 而*H. pylori*血清学试验阴性的人群也患有GHP. 因此, 有研究表示*H. pylori*与GHP的发生无明显相关性[3,11,12,25,26]. 这些研究说明还有其他因素导致GHP的持续存在, 其原因还有待于进一步研究.

4.2 自身免疫性胃炎与GHP发生的关系 Dirschmid等[27]的研究表明, 自身免疫性胃炎与GHP的发生密切相关. 而且长期以来自身免疫性胃炎被认为是一种癌前病变[20,27].

4.3 长期应用质子泵抑制剂与GHP发生的关系 Pashankar等[28]研究表明长期应用质子泵抑制剂(特别是儿童), 容易引发胃息肉. 目前大量研究表明长期应用质子泵抑制剂可以诱发胃底腺息肉. 在Carmack等[25]对美国120 000例患者的食管、胃、十二指肠镜检中, 胃息肉的患病率占6.35%, 胃底腺息肉的患病率最高, 占患者数的77%, 但未见肠上皮化生(intestinal metaplasia, IM). GHP的患病率为17%, 其中发生IM占13%. 他们推断胃底腺息肉的患病率明显增高, GHP的患病率显著降低是广泛使用质子泵抑制剂的结果[25]. *H. pylori*感染率和萎缩性胃炎的患病率持续降低可能是GHP相对降低的原因[25]. 许多研究表明东亚地区的研究数据可能不能应用于北美的疾病分类学研究中. 有文献同样报道胃息肉的多发类型因地理位置不同而发生改变. 东欧和亚洲GHP的发生率高于西方国家[29]. Carmack等[25]研究中也表明, 在西方国家, 胃底腺息肉的患病率逐渐上升, 主要原因是由于长期应用质子泵抑制剂治疗由*H. pylori*感染而引发的胃炎. GHP发生与长期应用质子泵抑制剂的关系尚不清楚. 如果GHP确实与*H. pylori*关系密切, 质子泵抑制剂是根除*H. pylori*的主要治疗方法, 长期应用质子泵抑制剂便可降低GHP的发生率. 但在GHP发生机制还不明确的今天, 此结论还需要进一步论证.

4.4 器官移植与GHP发生的关系 Jewell等[26]对器官移植受体发生GHP的研究表明, GHP的发生与器官移植有明显的关联性. 由于器官移植受体患者需要在术后应用免疫抑制药物, 自身免疫抑制容易并发感染, 慢性胃炎的发生率高于正常人群, 这可能是GHP容易发生在器官移植受体患者的主要原因. 器官移植受体患者的GHP和非器官移植患者的GHP相比较, 其组织病理学特征无明显差异, 也在一定程度上表明两者的病理学发生极有可能是相同的. 但是器官移植受体患者容易发生GHP的明确发病机制还有待于进一步的研究.

5 GHP不典型增生或癌变

GHP最初通常被认为是一种良性病变, 但是目前越来越多的研究报道GHP伴有不典型增生的发生率是1%-20%[13,19,30-34], GHP伴有局灶癌变的发生率是0.3%-7.1%[1,19,32,35,36]. GHP发生局部癌变的癌组织通常是高分化癌, 但也有一些报道证实GHP发生局部癌变的癌组织为印戒细胞癌

■研发前沿
靶向治疗是目前分子生物学的研究热点. 通过分子水平对粘蛋白调控作用机制的不断研究, 粘蛋白有可能成为GHP有效的基因靶点.

■相关报道
近期有篇关于粘蛋白的报道, 显示在GHP伴低级别不典型增生(low grade dysplasia, LGD)、GHP伴低级别不典型增生(high grade dysplasia, HGD)或癌变的患者中, MUC1的表达模式不同, 所有正常的胃黏膜和85.6%的未伴有不典型增生的GHP, MUC1在细胞质和细胞膜弥漫阳性; 在80%的GHP伴LGD和100%的GHP伴HGD或癌变其MUC1在腔缘侧细胞膜阳性(P<0.001). 即MUC1表达模式2的GHP更具有恶变潜能. 该篇文章从粘蛋白的表达模式揭示GHP的恶变潜能, 新颖, 有实际意义.

(低分化癌)[37,38]. 之前有文献证实, 与消化系的其他息肉类似, 越大的GHP(特别是>2 cm的GHP)发生癌变的危险性越高[32,39,40]. 因此, 研究表明>2 cm的GHP应该被完全切除[41]. 同时, 有文献表明, <2 cm的GHP同样具有癌变潜能[30,42]. 另有一些文章表明, >0.5 cm的GHP均应被切除[43]. 然而, GHP毕竟是一种癌变率较低的病变, 我们还不能将GHP看做是一种癌前病变. 但这样的做法可能是不实用的. 因此, 找出一些在GHP发生癌变时特征性的标志物是GHP研究的重点内容.

6 GHP的分子生物学研究

目前为止, 有关GHP的研究均为小样本分析GHP与胃癌发生的特异性通路的关系. 有一些学者对伴有不典型增生或局灶癌变的GHP患者进行了相关分子生物学的研究. *p53*抑癌基因通过诱导细胞凋亡抑制癌症的发展. *p53*基因的突变和/或蛋白聚集是人类肿瘤(特别是消化系肿瘤)发生最常见的改变之一. 由于杂合子缺失、移码突变等原因, 使得*p53*基因失活, 肿瘤形成[44,45].

有研究显示与正常和增生的胃黏膜相比, 在不典型增生的区域中P53的阳性率明显增加[32,35,46-48]. 并且推测P53的阳性表达在未伴不典型增生或局灶癌变的GHP发展至GHP伴有不典型增生再发展到GHP伴有局灶癌变(GHP-GHP伴有不典型增生-GHP伴局灶癌变)的过程中是一个晚期事件[32,35,46-48]. Murakami等[35]的研究显示, 在GHP-GHP伴有不典型增生-GHP伴有局灶癌变的过程中, P53的阳性表达率逐渐增加, 同时还表明P53的标记指数与GHP的大小具有明显的相关性. 但是, P53在GHP中表达的研究仍存在争议. 在Dijkhuizen等[49]的研究中, P53在GHP的表达呈阴性. Dijkhuizen等[49]同时研究了MDM2以及感染了巨细胞病毒和EB病毒患者的情况, 所有这些研究结果*p53*表达均为阴性. 以上研究结果的不同可能是由于样本数量不同所造成的. Dijkhuizen等[49]研究发现GHP中存在*k-ras*基因的突变. Murakami等[35]的研究显示6%的GHP患者存在*k-ras*基因的突变[32,49]. Dijkhuizen等[49]推断单独的*k-ras*基因突变并不能引起GHP发生肿瘤性转换, 因为在未伴不典型增生或癌变的GHP中同样检测到了*k-ras*基因的突变.

在GHP伴有不典型增生的患者中, 一些学者研究了微卫星的不稳定性(microsatellite instability, MSI), 其发生0%-16.7%[47]. 虽然Nogueira等[47]证实GHP中存在MSI, 但是他并不能解释GHP发生恶性转换与MSI的关系. Weiss等[50]应用基因组杂交方法分析3例GHP和8例腺瘤, 发现所有患者均检测到染色体异常. 腺瘤的染色体异常发生在7q36、20q12和5q14-q21. GHP的染色体异常见于15q11-14、1p21-31和21q11-21.2. 在GHP和腺瘤中均频繁发现9p21.3的染色体缺失. 他们表示, 在胃的癌前病变的研究中, 同样检测到以上染色体的异常, 说明以上染色体异常与胃癌的发生相关. 因此, 他们断言在胃癌的发生中存在双通路概念-GHP通路和腺瘤通路.

Ki-67可作为反映细胞增殖活性的重要指标. 通过Ki-67的表达可以帮助我们判断GHP细胞的增殖情况. Murakami等[35]对GHP细胞中的Ki-67标记指数情况的研究表明, GHP细胞中的Ki-67标记指数明显高于正常胃黏膜细胞, 其差异具有统计学意义. 在GHP伴高级别不典型增生(high grade dysplasia, HGD)的Ki-67标记指数明显高于未伴不典型增生的GHP或GHP伴低级别不典型增生(low grade dysplasia, LGD)的Ki-67标记指数, 其差异具有统计学意义. 在一例对GHP伴印戒细胞癌的研究结果显示, Ki-67在癌组织和癌组织周围的小凹上皮细胞中的阳性率分别为72.3%和70.5%, 但是在距癌组织较远处的小凹上皮细胞中的阳性表达率仅4.5%[11].

Murakami等[35]研究了$p21^{WAF1/CIP1}$和Cyclin D1在GHP的表达情况. 他们证实, 在GHP-GHP伴有不典型增生-GHP伴有局灶癌变的过程中, $p21^{WAF1/CIP1}$和Cyclin D1的表达逐渐减少.

其他学者也试图研究其他的标志物(如: ERB-2, APC, DCC, LOH)以阐明GHP发生癌变的机制[32,47,49]. 然而, 目前为止未发现提示GHP癌变有价值的标志物.

7 GHP与粘蛋白表型的关系

粘蛋白(mucin, MUC)是一类高分子量的糖蛋白, 目前已发现20种MUC. 根据其结构和功能分为分泌型和膜结合型2大类[51]. 分泌型粘蛋白包括MUC2、MUC5AC、MUC5B、MUC6、MUC7、MUC8、MUC9和MUC19. 编码前四种蛋白的基因位于染色体11q15.5上. 这些MUC在维持胃肠道正常的生理过程、肿瘤的发生、发展及转移中扮演着重要的角色[51]. MUC1是克隆最早的跨膜粘蛋白, 定位于染色体1q21-24[52,53]. MUC1在许多分泌型上皮细胞的顶端表达[51]. MUC2主要表达于小肠和结肠

的杯状细胞中[52,54,55]. MUC3主要表达在胃肠道上皮细胞中, 其基因定位于染色体7q22[51]. 胃癌组织中, MUC3的阳性表达与患者的不良预后相关[56]. MUC5AC主要表达在胃肠道和支气管上皮细胞中, 在胃小凹上皮细胞呈高表达[57]. MUC5B主要表达在支气管、唾液腺和食管上皮中. MUC6主要表达在胃及十二指肠的黏液腺体中[58,59].

越来越多的研究报道了胃癌的发生、预后以及临床病理学因素与MUC1、MUC2、MUC3、MUC5AC和MUC6的表达相关[56,60-68]. 也有研究显示在GHP伴LGD、GHP伴HGD和GHP伴局灶癌变的患者中MUC5AC的表达量逐渐减少. 与未伴有不典型增生或癌变的GHP相比, MUC2在GHP伴有不典型增生或局部癌变的患者中表达量明显升高[44,68].

近期有研究表明在GHP伴LGD、GHP伴HGD或癌变的患者中, MUC1的表达模式不同. 在所有正常的胃黏膜和85.6%未伴有不典型增生的GHP中, MUC1为第一种表达模式: 在细胞质和细胞膜弥漫阳性. 在80%GHP伴LGD和100%GHP伴HGD或癌变中, MUC1为第二种表达模式: 在腔缘侧细胞膜阳性(P<0.001)[68]. 此研究结果还证实, 在伴有不典型增生或癌变的GHP中MUC1的表达与未伴有不典型增生或癌变的GHP中相比, MUC1的表达多呈第二种表达模式(P<0.01), 但此种表达模式的发生机制还没有明确的结论.

许多研究已经表明在各种炎性或恶性疾病中均可检测到粘蛋白的异常表达. 粘蛋白的表达与恶性疾病的进展具有一定的相关性[51]. 粘蛋白可以作为一种区分正常和病变组织的良好标志物[51].

8 结论

GHP是胃中最常见的息肉类型, 他不同于结肠直肠的增生性息肉. GHP是胃黏膜病变的警钟. 近年来一些研究已经证实GHP具有一定的癌变潜能. 有一些研究结果提示GHP的癌变过程为: GHP→不典型增生→局灶癌变. 从遗传学角度对GHP的研究很少, 虽然一些研究试图寻找能特征性提示GHP将发生恶性转变的标志物, 但是至今仍未发现. 粘蛋白可能是在恶性肿瘤的早期阶段检测、治疗及提示肿瘤预后的良好标志物. 研究GHP的遗传学和粘蛋白的表达情况可能是将来研究的重点内容.

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■创新盘点

粘蛋白在肿瘤的早期诊断、判断预后及临床治疗等方面具有一定意义, 可作为判断GHP恶性潜能的参考指标. GHP伴LGD、GHP伴HGD和GHP伴局灶癌变的患者中MUC5AC的表达量逐渐减少, 与未伴有不典型增生或癌变的GHP相比, MUC2在GHP伴有不典型增生或局部癌变的患者中表达量明显升高. 粘蛋白在肿瘤的早期诊断、判断预后及临床治疗等方面具有一定意义, 可作为判断GHP恶性潜能的参考指标.

■应用要点
研究GHP的发病机制可以揭示GHP的发生、发展规律. 在GHP恶变的早期诊断方面具有一定意义.

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■同行评价
本文选题很新颖, 具有一定的临床意义.

编辑 李军亮 电编 闫晋利