结直肠神经内分泌癌研究进展

马向涛

关键词:结直肠癌;神经内分泌;预后
中图分类号:R735.3 文献标识码:A 文章编号:1000-8578(2008)01-0073-03

0 引言

神经内分泌细胞遍布全身,主要分布于胃肠道、胰腺、肺、甲状腺、肾上腺以及其他许多器官。结直肠神经内分泌癌(Neuroendocrine Carcinoma, NEC)是一类以神经内分泌细胞构成的恶性肿瘤,以具有独特的激素合成和分泌功能以其分化差、侵袭性强、转移早等恶性潜能而逐渐为人们所重视[1]。本文就结直肠神经内分泌癌生物学特性以及诊断与治疗进展进行综述。

收稿日期:2007-01-09;修回日期:2007-05-14
资助项目:北京市优秀人才培养资助项目(20061D0900500347)
作者单位:100080 北京海淀医院外科
作者简介:马向涛(1972-),男,博士,副主任医师,主要从事消化道肿瘤分子生物学研究

1 生物学特征与临床表现

结直肠神经内分泌癌发病率所占比例从0.6%～3.9%不等。Saclarides 等[2]报道 988 例中有 39 例(3.9%)为结肠神经内分泌癌,Bernick 等[3]研究了 6495 例结直肠癌标本,共发现 38 例(0.6%)神经内分泌癌,发病率差别较大的原因主要是诊断标准不统一。男性多于女性,比例为 1～5∶1,年龄分布于 28～89 岁,多见于 60～70 岁。发生部位主要在

metastatic colorectal cancer: the NO16966 trial[J]. J Clin Oncol, 2006, 6(4): 261-264.
[9] Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluoroutacil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group[J]. N Engl J Med, 2000, 343(13):905-914.
[10] Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicenter randomized trial[J]. Lancet, 2000, 355(9209):1041-1047.
[11] Fuchs C, Mitchell EP, Hoff PM. Irinotecan in the treatment of colorectal cancer[J]. Cancer Treat Rev, 2006, 32(7):491-503.
[12] Cvitkovic E, Bekradda M. Oxaliplatin: A new therapeutic option in colorectal cancer[J]. Semin Oncol, 1999, 26(6):647.
[13] de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer[J]. J Clin Oncol, 2000, 18(16): 2938-2947.
[14] Colucci G, Gebbia V, Paoletti G, et al. Phase Ⅲ Randomized Trail of FOLFIRI Versus FOLFOX4 in the treatment of Advanced Colorectal Cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale[J]. J Clin Oncol, 2005, 23(22):4866-4875.
[15] Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study[J]. J Clin Oncol, 2004, 22(2):229-237.
[16] Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line[J]. J Clin Oncol. 2005, 23(36):9441-9442.
[17] Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment[J]. J Clin Oncol, 2004, 22(7):1209-1214.
[18] Gorthey A. The continuum of care in colorectal cancer: Eliminating the concept of distinct lines of treatment[M]. The American Society of Clinical Oncology, 2007. 224-228.
[19] Paulo M Hoff, MD, FACP, et al. Intense versus minimal first-line therapy in metastatic colorectal cancer[M]. The American Society of Clinical Oncology, 2007. 220-223.
[20] Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer-A GERCOR study[J]. J Clin Oncol, 2006, 24(3):394-400.
[21] Labianca R, Floriani I, Cortesi E, et al. Alternative versus continueous "FOLFIRI" in advanced colorectal cancer (ACC): A randomized "GISCAD" trial[J]. Proc Am Soc Clin Oncol, 2006, 24(147s): abstr 3505.
[22] Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan - refractory metastatic colorectal cancer[J]. N Engl J Med, 2004, 351(4): 337-345.
[23] Saltz L, Lenz H, Kindler HL, et al. Interim report of randomized phase Ⅱ trial of cetuximab/becacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer[J]. Proc Am Soc Clin Oncol, 2005, abstr 169b.
[24] Van Cutsem E, Nowaci M, Cascinu S, et al. Randomized phase Ⅲ study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (MCRC): the CRYSTAL trial[J]. J Clin Oncol, 2007, 25 (18s):4000.
[25] Tappenden P, Jones R, Paisley S, et al. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer[J]. Health Technol Assess(Winchester, England), 2007, 11(12):1-128.

[编辑:周永红;校对:马福元]

乙状结肠与直肠,其次为盲肠,很少发生于横结肠、降结肠。

结直肠神经内分泌癌具有恶性程度高、侵蚀性强、转移早的生物学特性。文献报道 80 %～93.4 %的结直肠神经内分泌癌确诊时已经出现不同程度的转移,其中79.2 %发生区域淋巴结转移,38.5 %～62.5 %的患者出现肝转移[4,5]。结直肠神经内分泌癌生物学特性除了与结直肠恶性肿瘤具有的共同生物学特性外,还具有合成、储存和分泌肽类和(或)胺类激素的功能,如嗜铬素、人绒毛膜促性腺激素、5-羟色胺、胰高血糖素、胃泌素及生长抑素等 40 余种,结直肠神经内分泌癌分泌的常见激素依次为血清素、生长抑素与胃泌素,临床上可以引起相应的内分泌紊乱症状[7,8]。

结直肠神经内分泌癌临床症状多不典型,与一般结直肠肿瘤无明显差异,诸如大便习惯改变、便血、腹痛、体重下降及全身不适等。有学者报道了以异位 ACTH 综合征、顽固性高钙血症以及伴有严重分泌性腹泻为首发症状的结肠神经内分泌癌。但只有1.6 %的患者合并明显的内分泌紊乱症状,原因可能有以下几点:①肿瘤产生的活性物质不足以对靶器官产生效应;②肿瘤产生的活性物质在外周血中很快被降解;③肿瘤分泌的可能为激素前体物质,其生物学活性不如其终产物,且肿瘤本身分泌能抑制其活性的对抗产物[9-12]。

2　辅助检查

除了常规检查外,对于结直肠神经内分泌癌患者有些检查是非常重要的:(1)内窥镜检查:对于诊断结直肠肿瘤,内窥镜的作用非常重要,不仅可以明确肿瘤部位、大小、形状,还可以进行活组织检查定性诊断。Bernick 等[3]报道术前活检可以对59.3 %的患者做出正确诊断;(2)影像学检查:首选 CT 以重点排除胸腹部淋巴结转移,对于可疑患者,应将腹部 CT 作为常规检查。而对于有症状或可疑其他部位转移者,进一步行相应检查,如对于可疑骨转移者行核素骨扫描;(3)血清肿瘤标记物:除常规的 CEA、AFP、CA19-9 等检查外,血清嗜铬素(CgA)检查可能会对神经内分泌癌的诊断有重要意义。研究显示:在 81 %的神经内分泌癌患者中,其血清 CgA 水平高于正常,而 CgA 恰恰是神经内分泌细胞中分泌颗粒所释放的代表其分泌特征的物质[13]。鉴于结直肠神经内分泌癌的高度恶性以及治疗方法上的差异,虽然其发病率不高,但仍可将其作为一种常规肿瘤标记物加以检测;(4)激素及其相关产物的检测:对于有内分泌症状的肠道肿瘤患者,应根据其相应症状监测其体内相关激素及其前体或代谢产物。对患者体内激素及其相关产物的监测对于疾病诊断、指导治疗、判断肿瘤的增长与复发都有着重要的意义[14]。

3　病理学特征

结直肠神经内分泌癌根据细胞分化程度分为 3 型[15]:(1)高分化神经内分泌癌:其组织学表现与类癌相似,但异型性明显,可见组织坏死及血管侵犯;(2)中间型神经内分泌癌:细胞大小为典型小细胞的 2 倍,胞浆丰富,外周有分隔,染色适中;(3)小细胞神经内分泌癌:细胞直径 12～15 μm,是神经内分泌癌中分化最差的一种。镜下可见大量核分裂像,胞浆染色浓密且明显异常,胞浆稀少,其组织学类似于肺小细胞癌。

免疫组织化学染色对结直肠神经内分泌癌研究有着重要意义。神经内分泌癌最具代表性的是细胞内致密核颗粒(分泌颗粒),在表达 CgA 的细胞中都能发现其存在,这一点更能说明 CgA 在诊断结直肠神经内分泌癌中的意义。CgA 来自肾上腺髓质嗜铬细胞神经分泌颗粒中,与儿茶酚胺类神经肽及肽类激素共同贮存于细胞神经内分泌颗粒中,被认为是神经内分泌分化的理想标记物。此外神经元特异性烯醇酶、突触素、胃泌素、人绒毛膜促性腺激素、5-羟色胺、Leu-7、神经降压素、上皮膜抗原等多种标记物多被用于神经内分泌癌诊断[16]。

4　诊断与鉴别诊断

神经内分泌癌最终诊断仍需靠病理学确定,其诊断方法如下[3-5]:(1)临床症状:由于很多神经内分泌肿瘤所释放的神经肽不引起明显症状,因此出现相应激素过剩症状或血中某种激素水平升高只作为诊断参考,但无症状患者不能排除本病;(2)常规染色:肿瘤为小细胞未分化癌或类癌图像,间质血管丰富,瘤细胞呈弥漫性分布或不同程度器官样结构者,结合其他条件对诊断常见低分化癌或单纯癌图像不够典型者,应考虑神经内分泌癌的可能,做进一步观察;(3)亲银及嗜银染色:怀疑有神经内分泌癌可能性时,应做亲银及嗜银染色。亲银和(或)嗜银染色阳性者可考虑神经内分泌癌。进一步做免疫组化和(或)电镜观察;(4)神经内分泌免疫组化染色观察:目前常用的标记物有神经元特异性烯醇酶、嗜铬素、Leu-7、突触素等。一般主张用两种染色结果结合分析的方法,如为阳性可确定诊断。但有的神经内分泌癌胞浆分泌颗粒稀少,免疫组化可不着色或着色淡,这种情况下电镜观察胞浆分泌颗粒有助于诊断;

(5)电镜观察:电镜观察胞浆神经内分泌颗粒也可帮助确诊,根据胞浆分泌颗粒的形态特点进行分析也可做出激素功能诊断。电镜诊断有一定特异性,但不能观察瘤细胞的分布。一般采用银染、免疫组化和(或)电镜观察结合分析的方法达到确诊;(6)确诊为神经内分泌肿瘤后,可进一步应用免疫组化、电镜观察方法对肿瘤的激素功能类型进行诊断;(7)肿瘤的良恶性及恶性程度的诊断标准同其他内分泌及神经系统肿瘤。

5 治疗与预后

结直肠神经内分泌癌治疗原则包括手术、化疗及放疗。(1)手术:对于结直肠神经内分泌癌治疗仍以手术为主,手术原则基本遵循胃肠道常见恶性肿瘤的治疗原则;(2)化疗:根据其形态及生物学特性与肺小细胞癌相似这一特征,应用依托泊甙与顺铂联合治疗结直肠神经内分泌癌取得一定疗效。此方案对低分化神经内分泌癌的治疗有明确效果,而高分化者对其无反应。在低分化神经内分泌癌治疗中,部分缓解率为 67 %,完全缓解率为 17 %,平均生存时间为 19 个月[17];(3)放疗:结直肠神经内分泌癌患者接受放射治疗,但具体疗效无相关数据报道。

结直肠神经内分泌癌由于其分化差、侵袭性强、转移早,因此预后不良。目前考虑与下列因素有关:(1)神经内分泌细胞由不成熟的肿瘤干细胞分化而来;(2)癌细胞可能自身分泌一些物质促进肿瘤细胞生长、增殖和转移。80 %～93.4 %的患者在就诊时已出现不同程度的远处转移。文献报道 1 例患者最长存活263.7个月,平均生存时间10.4个月。6 个月、1 年、2 年、3 年与 5 年生存率分别为 58 %、46 %、26 %、13 %与 6 %[18-20]。

参考文献:

[1] Staren ED, Gould VE, Warren WH, et al. Neuroendocrine carcinomas of the colon and rectum: a clinicopathologic evaluation[J]. Surgery, 1988, 104(6):1080-1089.

[2] Saclarides TJ, Szeluga D, Staren ED. Neuroendocrine cancers of the colon and rectum: results of a ten-year experience[J]. Dis Colon Rectum, 1994, 37(7):635-642.

[3] Bernick PE, Klimstra DS, Shia J, et al. Neuroendocrine carcinomas of the colon and rectum[J]. Dis Colon Rectum, 2004, 47(2):163-169.

[4] Staren ED, Gould VE, Jansson DS, et al. Neuroendocrine differentiation in "poorly differentiated" colon carcinomas[J]. Am Surg, 1990, 56(7):412-419.

[5] Gould VE, Jao W, Chejfec G, et al. Neuroendocrine carcinomas of the gastrointestinal tract[J]. Semin Diagn Pathol, 1984, 1(1):13-18.

[6] Atasoy P, Ensari A, Demirci S, et al. Neuroendocrine differentiation in colorectal carcinomas: assessing its prognostic significance[J]. Tumori, 2003, 89(1):49-53.

[7] Vortmeyer AO, Lubensky IA, Merino MJ, et al. Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas[J]. J Natl Cancer Inst, 1997, 89(19):1448-1453.

[8] Grabowski P, Schonfelder J, Ahnert-Hilger G, et al. Expression of neuroendocrine markers: a signature of human undifferentiated carcinoma of the colon and rectum[J]. Virchows Arch, 2002, 441(3):256-263.

[9] Khansur TK, Routh A, Mihas TA, et al. Syndrome of inappropriate ADH secretion and diplopia: oat cell (small cell) rectal carcinoma metastatic to the central nervous system[J]. Am J Gastroenterol, 1995, 90(7):1173-1174.

[10] Hung SS. Small cell carcinoma of the colon. A case report and literature review[J]. J Clin Gastroenterol, 1989, 11(3):335-339.

[11] Sakata J, Wakai T, Shirai Y, et al. Humoral hypercalcemia complicating adenocarcinoma of the sigmoid colon: report of a case[J]. Surg Today, 2005, 35(8):692-695.

[12] Cebrian J, Larach SW, Ferrara A, et al. Small-cell carcinoma of the rectum: report of two cases[J]. Dis Colon Rectum, 1999, 42(2):274-277.

[13] DiSario JA, Burt RW, Kendrick ML, et al. Colorectal cancers of rare histologic types compared with adenocarcinomas[J]. Dis Colon Rectum, 1994, 37(12):1277-1280.

[14] Shinji S, Naito Z, Ishiwata T, et al. Neuroendocrine cell differentiation of poorly differentiated colorectal adenocarcinoma correlates with liver metastasis[J]. Int J Oncol, 2006, 29(2):357-364.

[15] Gaffey MJ, Mills SE, Lack EE. Neuroendocrine carcinoma of the colon and rectum. A clinicopathologic, ultrastructural, and immunohistochemical study of 24 cases[J]. Am J Surg Pathol, 1990, 14(11):1010-1023.

[16] Helpap B, Kollermann J. Immunohistochemical analysis of the proliferative activity of neuroendocrine tumors from various organs. Are there indications for a neuroendocrine tumor-carcinoma sequence?[J]. Virchows Arch, 2001, 438(1):86-91.

[17] Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms[J]. Cancer, 1991, 68(2):227-232.

[18] Kumarasinghe MP, Weng EK. Pathological features and their prognostic implications in colorectal endocrine cell tumours: a long-term follow-up study[J]. Pathology, 2005, 37(3):204-210.

[19] Akintola-Ogunremi O, Pfeifer JD, Tan BR, et al. Analysis of protein expression and gene mutation of c-kit in colorectal neuroendocrine carcinomas[J]. Am J Surg Pathol, 2003, 27(12):1551-1558.

[20] Grabowski P, Schindler I, Anagnostopoulos I, et al. Neuroendocrine differentiation is a relevant prognostic factor in stage Ⅲ/Ⅳ colorectal cancer[J]. Eur J Gastroenterol Hepatol, 2001, 13(4):405-411.

[编辑:安 凤;校对:马福元]