

G Chir Vol. 30 - n. 3 - pp. 87-92
Marzo 2009

articolo originale

Sporadic flat ileal adenocarcinoma: an intriguing challenge in the comprehension of a rare neoplasia and its genesis. Case report and review of literature

S. ERRA, D. COSTAMAGNA¹, G. BOTTO¹, C. GEMME², R. DURANDO¹

SUMMARY: Sporadic flat ileal adenocarcinoma: an intriguing challenge in the comprehension of a rare neoplasia and its genesis. Case report and review of literature.

S. ERRA, D. COSTAMAGNA, G. BOTTO, C. GEMME, R. DURANDO

Small bowel adenocarcinoma is a rare tumor, with a still not well studied tumorigenesis process, usually presenting in an advanced stage. The clinical diagnosis is often difficult; surgery is the treatment of choice when feasible, while the chemotherapeutic approach is still not well codified.

We describe the case of a 71-yr-old male patient, presenting with an acute right abdomen. At laparotomy the terminal ileum appeared chronically inflamed and thickened. An ileocecal resection with latero-lateral ileocolic anastomosis was performed. The gross appearance resembled an inflammatory bowel disease, but microscopic examination revealed the extensive presence of an infiltrating ileal adenocarcinoma.

Literature about small bowel adenocarcinoma has been reviewed for better understanding its pathogenesis.

RIASSUNTO: Adenocarcinoma piatto sporadico dell'ileo: una sfida intrigante nella comprensione di una neoplasia rara e della sua genesi. Descrizione di un caso e revisione della letteratura.

S. ERRA, D. COSTAMAGNA, G. BOTTO, C. GEMME, R. DURANDO

L'adenocarcinoma dell'intestino tenue è un tumore raro, con un processo di tumorigenesi non ancora ben studiato e che di solito si presenta in uno stadio avanzato. La diagnosi clinica è di regola difficile; la chirurgia è il trattamento di scelta, quando possibile, mentre l'approccio chemioterapico non è ancora ben codificato.

Descriviamo il caso di un paziente di 71 anni giunto alla nostra osservazione con quadro di addome acuto destro. Alla laparotomia, l'ileo terminale era infiammato ed ispessito. Si eseguiva una resezione ileo-ciecale, con anastomosi ileocolica latero-laterale. L'aspetto macroscopico era quello di una malattia infiammatoria intestinale, ma l'esame microscopico rivelava la presenza estesa di un adenocarcinoma infiltrante ileale.

Si è proceduto ad un'analisi della letteratura sull'adenocarcinoma del piccolo intestino, con l'intento di comprenderne meglio la patogenesi.

KEY WORDS: Small bowel - Adenocarcinoma - Tumorigenesis - Cdx2 - EGFR.
Intestino tenue - Adenocarcinoma - Tumorigenesi - Cdx2 - EGFR.

Introduction

Adenocarcinomas of the small bowel (SBA) are rare cancers comprising 0.1 to 0.3% of all malignancies (1). Recent data suggest that the annual incidence of SBA is in the range of 2.2-5.7/million population/year in the Western countries (2). This paucity of cases has resulted in few systematic researches on the pathogenesis, natural history and treatment of SBA (1, 2).

Despite the fact that the small intestine has the lar-

gest mucosal surface area in the gastrointestinal (GI) tract (more than 90%), it is the site of only 2% of all primary GI tumors. SBAs represent approximately 25% of all small bowel neoplasms (benign and malignant) and 30-50% of all malignant tumors of small bowel. The SBA incidence is only one-fortieth to one-fiftieth in comparison with the incidence of the adenocarcinoma of the large intestine (3).

The small bowel appears to be relatively resistant to the development of tumors. A variety of factors have been proposed to explain the rare occurrence of SBA, such as the rapid small bowel transit, the large volume of secretions reducing the intraluminal concentration of carcinogens, the low level of bacteria compared to the colon minimizing the formation of procarcinogens from the degradation of bile salts, the high turnover of small bowel mucosal cells inhibiting competitively the growth of malignant cells, finally the high level of IgA (4, 5).

"Santo Spirito" Hospital, Casale Monferrato (AL), Italy
Department of Pathology and Anatomy

¹ General Surgery Department

² Gastrointestinal Endoscopy Unit

© Copyright 2009, CIC Edizioni Internazionali, Roma

The four major types of primary small bowel malignancies are adenocarcinoma, sarcoma, carcinoid tumors, and lymphomas, of which the most prevalent is adenocarcinoma (6). The peak incidence of SBA is reported to occur in the 6th and 7th decades (7). The most common onset symptoms are abdominal pain, gastrointestinal bleeding and weight loss. The obstruction is frequent and it is typically intermittent. The average duration of symptoms before diagnosis is between 6 and 12 months. Most intestinal carcinomas are infiltrative tumors and have a high tendency to circumferential spread through the intestinal wall. Tumor size at surgery ranges from 1-9 cm with a mean of 4.5 cm (7). Long stenosis is uncommon. Milman and Gallego described two cases of "long" SBA (respectively 10 and 20 cm) involving the terminal ileum, simulating Crohn's disease, with irregular narrowing and thickening of the wall (8, 9). Less frequently, the tumor grows into the lumen as a polypoid lesion (8). Polypoid adenocarcinomas may present with intussusception (7). Early adenocarcinomas in the small intestine are a rare entity. Only 3-10% of SBA are found in stage T1 and 0-3% in stage Tis (10). The lack of specific symptoms and rarity of SBA contribute to advanced-stage presentation (11). Among patients staged according to the American Joint Committee on Cancer (AJCC) schema, 2.7% were stage 0, 12% stage I, 27% stage II, 26% stage III, and 32.3% stage IV (12). Howe et al. observed that patients with poorly differentiated tumors had a significantly decreased 5-year disease specific survival (DSS) (22.4%) compared with that for patients with well-differentiated tumors (39.4%) and moderately differentiated to well-differentiated tumors (33.3%) (13). Tumor stage is also significantly correlated with survival. In the AJCC stage groups, the DSS rate for patients with stage IV disease (4.2% 5-year DSS) was significantly worse than for patients with stage I-III disease (65.1% 5-year DSS for stage I disease, and 35.4% 5-year DSS for stage III disease) (13).

SAB are aggressive with poor 5-yr overall survival of around 20-30% in various studies. The survival is directly related to the potential for surgical resection with intent to cure (6). Because of the small number of published cases and the lack of appropriated randomized prospective studies, the optimal therapeutic strategy has not been exactly defined as yet (4). For localized disease, surgical resection is the mainstay of therapy because complete removal of tumor and of draining lymph nodes is one of the most important predictors of survival. The 5-year survival rate ranges from 40-60% in resected to 15-30% in non-resected patients. Limited small resection may also be indicated in metastatic disease to relieve local symptoms such as obstruction and tumor bleeding (4). Regarding adjuvant chemotherapy, neither the indication nor the optimal regimen has yet been exactly defined. Adjuvant chemotherapy is usual-

ly recommended in locally advanced tumors or in those with lymphatic spread. Because no advantage of adjuvant therapy for stage II disease in SBA has been demonstrated, Eigenbrod et al. do not see an indication for adjuvant treatment after resection of the primary tumor. They describe advantages only in patients with stage IV disease (4). Currently, chemotherapy regimens for SBA are extrapolated primarily from the experience with colorectal cancer or upper GI tract cancers, but this is clearly a suboptimal approach.

The increased understanding of the pathogenesis and tumorigenesis of SBA may provide potential candidates for therapeutic targets. A number of studies have reported biological markers implicated in SBA tumorigenesis, orienting to the development of molecular agents targeting critical pathways (2).

Case report

A 71-yr-old male patient was admitted to our Department for acute abdomen, with severe pain in the right iliac fossa. The patient was in good general status, and his medical history was unremarkable for significant pathologies, past malignancies, familiarity for intestinal tumors, environmental risk factors. Abdominal X-ray shows intestinal obstruction.

At surgery the terminal 20 cm of ileum appeared chronically inflamed and thickened. An ileocecal resection, involving 60 cm of bowel, with latero-lateral ileocolic anastomosis was performed.

The gross appearance resembled an inflammatory bowel disease (IBD) for the presence of various-sized, irregular mucosal ulcers, several elevated sessile nodules and fibrotic consistence of a 20 cm bowel wall. Microscopic examination of routine sections revealed the extensive presence of an infiltrating Not Otherwise Specified (NOS) adenocarcinoma. This lesion measured 20 cm in his greatest dimension; it was a moderately differentiated adenocarcinoma, infiltrating muscular layer, without regional lymph nodes metastasis. On the immunohistochemical study, the tumor expressed CEA (Fig. 1) and cytokeratin 20 (CK20), but it was negative for Cdx2 (Caudal-related homeobox2) and p53 oncoprotein.

EGFR (Epidermal Growth Factor Receptor) immunostaining reaction has been tested and revealed a focal and incomplete positivity (Fig. 2). The postoperative period was uneventful and the patient was discharged 7 days after the surgery. After eleven months the patient is alive without evidence of disease, undergoing regular oncological follow-up.

Discussion

The majority of SBA are histologically moderately to poorly-differentiated (14), and are found, in decreasing order of frequency, in the duodenum (47-55%), jejunum (18-29%), ileum (14-24%), and 14% in not specified sites (3,10). Duodenal adenocarcinomas usually arise in the periampullary region, suggesting that biliary secretion might play a role in tumor development. The ileum is an uncommon location for adenocarcinomas (3).

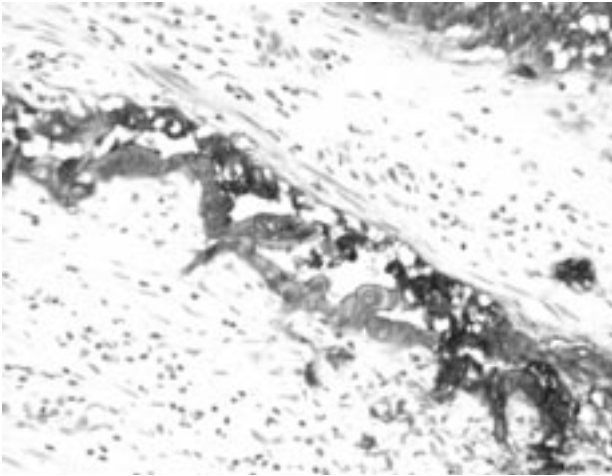


Fig. 1 - CEA immunohistochemical staining (10X).

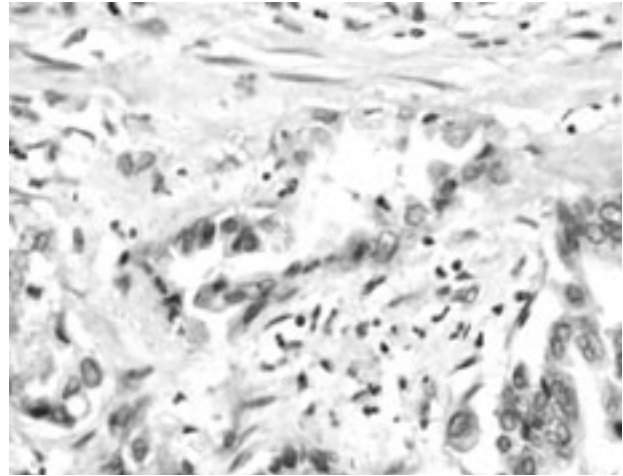


Fig. 2 - EGFR immunostaining reaction (20X): focal positive response.

Interesting observation is the very high rate of second malignancies in SBA patients. In a recent population-based study consisting of 10, 946 cases from 13 cancer registries, there was a 68% increase in the risk of a second primary cancer after SB carcinoma (15). The onset of SBA may signify a particularly unstable genomic situation, and may lead to a strong predisposition to additional malignancies (2).

Risk factors for SBA include hereditary gastrointestinal cancer syndromes (such as familial adenomatous polyposis, hereditary non-polyposis colorectal cancer syndrome or HNPCC and Peutz-Jeghers syndrome), inflammatory bowel disease (in particular Crohn's disease), cystic fibrosis, celiac disease, ileostomy, ileoanal pouch anastomosis (IPAA), cystoplasty, radiation therapy, and congenital bowel duplications (3, 16-21). Murphy et al. described an unusual case of Turcot's syndrome associated with ileal adenocarcinoma, intestinal non-Hodgkin's lymphoma, and duodenal adenocarcinoma (22). Neurofibromatosis and SBA association has also been described (23-25).

Further data suggest that SBA originate via an adenoma-carcinoma sequence, as described for colon cancer, with mutations in key growth regulating genes. Several epidemiological and pathological similarities have been identified between colorectal adenocarcinomas and SBA, leading to the hypothesis that some genetic mechanisms responsible for colorectal cancer (CRC) might also be involved in the development of SBA (3, 5). In a recent study, Onuma et al. reported a frequent phenotypic transformation from small intestinal epithelium into colonocytes in small intestinal adenomas and adenocarcinomas (26).

In 2005 Delaunoy et al. reviewed pathogenesis and risk factors of SBA, with the purpose of better under-

standing its molecular features and its similarities with CRC (3). Both tumor types usually arise from pre-existing adenomas, with an estimated one-third of solitary small bowel adenomas transforming into invasive carcinomas. SBA, as well as CRC, are most frequent in patients with a history of chronic inflammatory bowel disease and in patients with hereditary gastrointestinal cancer (3). *Ki-ras* is most frequently mutated on codon 12 in CRC, and is usually an early event in tumorigenesis. Available data show that *Ki-ras* mutations are observed in 14-83% of SBA cases, and particularly in duodenal locations (3). Codon 12 *Ki-ras* mutation is also found in 40-50% of small bowel adenomas, which is similar to that observed in large bowel locations (27). Rashid et al. demonstrated complete concordance in *Ki-ras* mutation between tissues from adenocarcinomas and contiguous adenomas in their cases, suggesting a relationship between the demonstrated adenoma-carcinoma sequence and *Ki-ras* mutation in SBA (28).

In CRC p53 mutation seems to be a rather late event in adenoma-carcinoma sequence. Similarly, it also appears as a late event in SBA development (29).

Other abnormalities have been detected in the expression of cell cycle-related proteins. As in CRC adenoma-carcinoma sequence, Arber et al. showed that overexpression of cyclin D1 and p27, as well as down-regulation of p16 and p21, appear early in the development of SBA (30). Smad-4 (Mothers against decapentaplegic homolog 4) protein, encoded by *Deleted Pancreatic Carcinoma (DPC4)* gene, is considered as a mediator of growth suppression via transforming growth factor β (TGF- β) signaling. Homozygous deletion or mutation of *DPC4* has been reported in about half of pancreatic ductal adenocarcinomas and in 3-50% of colorectal tumors (31, 32). Bläker et al. investigated dele-

tions of *DPC4* gene in a series of patients with SBA, founding missense mutations in 24% of tumors (33).

Defects in one or more *MMR* (mismatch repair) genes result in the microsatellite instability (MSI) phenotype in the HNPCC. Such *MMR* defects probably also contribute to SBA tumorigenesis, as suggested by the increased risk of SBA among HNPCC patients. The incidence of MSI observed in sporadic SBA varies in the literature from 11-18%, which is similar to that found in non-hereditary CRC (34). More than 80% of MSI tumors found in the colon carry MutL homologue 1 (*MLH1*) inactivation (35). Planck et al. have reported that only 50% of MSI tumors in the small bowel exhibit a *MLH1* defect (34). Brücher et al. have demonstrated that hypermethylation of human *MLH1*, *HPP1* (Human proto-homogene 1), *p14^{ARF}*, *p16^{INK4A}* and *APC* (Adenomatous Polyposis Coli), is a frequent finding in SBA. They suggest that hypermethylation plays a significant role in the molecular carcinogenesis of SBA, comparable with other gastrointestinal tumors (16).

Despite several similarities, some genetic events appear to be distinct between SBA and CRC. For instance, mutations and deletions of *APC* gene, as well as alteration in the so-called deleted colorectal cancer (*DCC*) gene are considered frequent early events in CRC, but occur rarely in SBA. However, reduced expression of β -catenin, without associated *APC* abnormality, was observed in SBA patients studied by Wheeler et al., suggesting β -catenin itself is mutated and able to induce SBA (36).

Lee et al. studied the expression of mucins (MUC) and cytokeratins (CK) in primary carcinomas of the digestive system. They found that CK20 was highly expressed in the colon (77%), appendix (100%), and anus cancers (80%). The rate of CK20 positivity in small bowel was 48%. The expression patterns of MUC1, MUC2, and CK20 were significantly different between the duodenum cancers and those of the remaining small intestine. The duodenum cancers showed MUC1+, MUC2-, and CK20-. On the other hand, jejunal and ileal cancers showed an opposite expression pattern, that is MUC1-, MUC2+, and CK20+. MUC1 and CK20 provide a significant distinction between right colon cancers (negativity) and left colon cancers (53% of positivity) (37).

Epidermal growth factor receptor belongs to the ErbB family. This family is comprised by transmembrane proteins that form part of the tyrosine kinase receptor proteins which are activated by different kinds of ligands. There are four different receptors in the ErbB family named ErbB1 (EGFR; HER or c-erbB, the first to be described), ErbB2 (HER2/neu), ErbB3 (HER3) and ErbB4 (HER4) (38). The oncogene *c-neu* is altered in approximately 50% of sporadic CRC. Zhu et al. reported that 60% of tumors in their patients series were po-

sitive for mutation, and the oncogene expression was seen to increase directly with tumor grade (39). Dysregulation of the EGFR signaling pathway because of EGFR overexpression, genetic aberrations, or other causes leads to malignant transformation. Recent studies have shown that EGFR expression is present in approximately 60% to 80% of colorectal carcinomas, and the receptor has emerged as a rational target for anticancer therapy in these tumors (40). EGFR positivity within the small intestine appeared to be almost entirely restricted to the proliferative (crypt) region (41). The role of EGFR in the tumorigenesis of SBA has not been defined as yet. We retain that it could be another possible area to investigate for the new of treatments of SBA, similarly to CRC.

In a recent study, Zhang et al. have immunohistochemically compared SBA with CRC for the expression of MUC1, MUC2, and MUC5AC, small-intestinal mucin antigen (SIMA), villin, and Cdx2. They found that MUC1 is similarly overexpressed in SBA and CRC. However, SBA exhibit more frequent loss of expression of MUC2 and less frequent overexpression of MUC5AC compared with CRC. The Authors observed that poorly differentiated SBA overexpress MUC1 more frequently than better differentiated SBA, stressing that up-regulation of MUC1 expression in CRC is a marker of poor prognosis. Furthermore they reported that SIMA and villin are also expressed in SBA. However, only half of the SBA included in this study showed SIMA immunoreactivity (and 80% of them displayed a focal staining pattern), while two third of SBA stained positively for villin (with 50% of focal response). These findings are in contrast with CRC in which diffuse SIMA and villin expression is demonstrated in the majority of the cases (42).

Cdx2 gene, which encodes a homeodomain transcription factor required for the development and maintenance of the intestinal epithelium, is a tumor suppressor in the colon ad rectum (43). A cardinal property defining tumor suppressors is their inactivation in cancer cells compared with normal cells. Cdx2 is not a classic tumor suppressor. In fact the study of Witek et al. shows that Cdx2 is overexpressed in most sporadic human colorectal tumors (>80% of CRC) compared with matched normal mucosa. Less than 20% of sporadic CRC exhibit reduced or absent Cdx2 expression. The precise mechanism underlying the overexpression of Cdx2 remains still undefined. It could represent a compensatory mechanism to reestablishing the equilibrium in proliferation and differentiation of the cell. Although Witek suggests the possibility that *Cdx2* could serve as an oncogene in the gastrointestinal tract, and its overexpression reflects the role in mediating euplastic transformation (43). Cdx2 expression has been examined in a limited number of SBA (44). In the study of Zhang, Cdx2 im-

munoreactivity is detected in only 60% of SBA, in contrast with 98% of CRC (42). Witek suggests the particular versatility of Cdx2 in regulating both proneoplastic and antineoplastic pathways and highlights the importance of further studies to define its complex role (43). We retain that it could be helpful also in the better comprehension of the tumorigenesis of SBA.

From the analysed literature about SBA, we could make many speculations about pathogenesis of observed ileal adenocarcinoma. We suppose that some sporadic somatic mutations have occurred in our patient only at ileal level, without involvement of colonic mucosa. In particular, the lack of expression of Cdx2 in our case can suggest a role of this tumor suppressor gene in carcinogenesis, inducing to suppose the existence of different mutations and different activation pathways for

the same gene. Finally we still remark the importance of better understanding of the pathogenesis and tumorigenesis of SBA in order to develop new therapeutic strategies for the future.

Acknowledgements

We express our gratitude to Silvio Modena, “Santo Spirito” Hospital of Casale Monferrato (AL), Italy, Pathological Anatomy Department Technical Coordinator; Eleonora Mazzoni, “Santo Spirito” Hospital of Casale Monferrato (AL), Italy, Pathological Anatomy Department; Carla Galea and Lorenzo Causarano, University of Turin, Medical and Surgical Disciplines Library, for their support and collaboration.

References

1. Fishman PN, Pond GR, Moore MJ, Oza A, Burkes RL, Siu LL, Feld R, Gallinger S, Greig P, Knox JJ. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. *Am J Clin Oncol* 2006;29:225-231.
2. Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. *Clin Oncol (R Coll Radiol)* 2007;19:143-149.
3. Delaunoy T, Neczyporenko F, Limburg PJ, Erlichman C. Pathogenesis and risk factors of small bowel adenocarcinoma: a colorectal cancer sibling? *Am J Gastroenterol* 2005;100:703-710.
4. Eigenbrod T, Kullmann F, Klebl F. Resection of small bowel adenocarcinoma liver metastasis combined with neoadjuvant and adjuvant chemotherapy results in extended disease-free period: a case report. *Int J Gastrointest Cancer* 2006;37:94-97.
5. Arber N, Neugut AI, Weinstein IB, Holt P. Molecular genetics of small bowel cancer. *Cancer Epidemiol Biomarkers Prev* 1997;6:745-748.
6. Verna D, Stroehlein JR. Adenocarcinoma of the small bowel: a 60-yr perspective derived from M. D. Anderson Cancer Center Tumor Registry. *Am J Gastroenterol* 2006;101:1647-1654.
7. Adler Sn, Lyon DT, Sullivan PD. Adenocarcinoma of the small bowel. Clinical features, similarity to regional enteritis, and analysis of 338 documented cases. *Am J Gastroenterol* 1982;77:326-330.
8. Gallego MS, Pulpeiro JR, Arenas A, Colina F. Primary adenocarcinoma of the terminal ileum simulating Crohn's disease. *Gastrointest Radiol* 1986;11:355-356.
9. Milman PJ, Gold BM, Bagla S, Thorn R. Primary ileal adenocarcinoma simulating Crohn's disease. *Gastrointest Radiol* 1980;5:55-58.
10. Friedrich-Rust M, Ell C. Early-stage small-bowel adenocarcinoma: a review of local endoscopic therapy. *Endoscopy* 2005;37:755-759.
11. Ugurlu MM, Asoglu O, Potter DD, Barnes SA, Harmsen WS, Donohue JH. Adenocarcinomas of the jejunum and ileum: a 25-year experience. *J Gastrointest Surg* 2005;9:1182-1188.
12. Stewart AK, Bland KI, McGinnis LS Jr, Morrow M, Eyre HJ. Clinical highlights from the National Cancer Data Base, 2000. *CA Cancer J Clin* 2000;50:171-183.
13. Howe JR, Karnell LH, Scott-Conner C. Small bowel sarcoma: analysis of survival from the National Cancer Data Base. *Ann Surg Oncol* 2001;8:496-508.
14. Abrahams NA, Halverson A, Fazio VW, Rybicki LA, Goldblum JR. Adenocarcinoma of the small bowel: a study of 37 cases with emphasis on histologic prognostic factors. *Dis Colon Rectum* 2002;45:1496-1502.
15. Scelo G, Boffetta P, Hemminki K, Pukkala E, Olsen JH, Andersen A, Tracey E, Brewster DH, McBride ML, Kliwer EV, Tonita JM, Pompe-Kirn V, Chia KS, Jonasson JG, Martos C, Colin D, Brennan P. Associations between small intestine cancer and other primary cancers: an international population-based study. *Int J Cancer* 2006;118:189-196.
16. Brucher BL, Geddert H, Langner C, Hoffer H, Fink U, Siewert JR, Sarbia M. Hypermethylation of hMLH1, HPP1, p14(ARF), p16(INK4A) and APC in primary adenocarcinomas of the small bowel. *Int J Cancer* 2006;119:1298-1302.
17. Potter DD, Murray JA, Donohue JH, Burgart LJ, Nagorney DM, van Heerden JA, Plevak MF, Zinsmeister AR, Thibodeau SN. The role of defective mismatch repair in small bowel adenocarcinoma in celiac disease. *Cancer Res* 2004;64:7073-7077.
18. Nagar A, Roberts IM. Small bowel diseases in the elderly. *Clin Geriatr Med* 1999;15:473-486.
19. Buckley JA, Siegelman SS, Jones B, Fishman EK. The accuracy of CT staging of small bowel adenocarcinoma: CT/pathologic correlation. *J Comput Assist Tomogr* 1997;21:986-991.
20. Hassan C, Zullo A, Speziale G, Stella F, Lorenzetti R, Morini S. Adenocarcinoma of the ileoanal pouch anastomosis: an emerging complication? *Int J Colorectal Dis* 2003;18:276-278.
21. Fichtner J. Follow-up after urinary diversion. *Urol Int* 1999;63:40-45.
22. Murphy HR, Taylor W, Ellis A, Sturgess R. An unusual case of Turcot's syndrome associated with ileal adenocarcinoma, intestinal non-Hodgkin's lymphoma, and duodenal adenocarcinoma. Review of the classification and genetic basis of Turcot's syndrome. *Fam Cancer* 2005;4:139-143.

23. Kingston RD. Neurofibromatosis and small bowel adenocarcinoma—an unrecognised association. *Gut* 1988;29:134.
24. Jones TJ, Marshall TL. Neurofibromatosis and small bowel adenocarcinoma: an unrecognised association. *Gut* 1987;28:1173-1176.
25. Joo YE, Kim HS, Choi SK, Rew JS, Park CS, Kim SJ. Primary duodenal adenocarcinoma associated with neurofibromatosis type 1. *J Gastroenterol* 2002;37:215-219.
26. Onuma EK, Amenta PS, Jukkola AF, Mohan V, Borra S, Das KM. A phenotypic change of small intestinal epithelium to colonocytes in small intestinal adenomas and adenocarcinomas. *Am J Gastroenterol* 2001;96:2480-2485.
27. Sutter T, Arber N, Moss SF, Findling RI, Neugut AI, Weinstein IB, Holt PR. Frequent K-ras mutations in small bowel adenocarcinomas. *Dig Dis Sci* 1996;41:115-118.
28. Rashid A, Hamilton SR. Genetic alterations in sporadic and Crohn's-associated adenocarcinomas of the small intestine. *Gastroenterology* 1997;113:127-135.
29. Vogelstein B, Fearon ER, Kern SE, Hamilton SR, Preisinger AC, Nakamura Y, White R. Allelotype of colorectal carcinomas. *Science* 1989;244:207-211.
30. Arber N, Hibshoosh H, Yasui W, Neugut AI, Hibshoosh A, Yao Y, Sgambato A, Yamamoto H, Shapira I, Rosenman D, Fabian I, Weinstein IB, Tahara E, Holt PR. Abnormalities in the expression of cell cycle-related proteins in tumors of the small bowel. *Cancer Epidemiol Biomarkers Prev* 1999;8:1101-1115.
31. Biankin AV, Morey AL, Lee CS, Kench JG, Binkin SA, Hook HC, Head DR, Hugh TB, Sutherland RL, Henshall SM. DPC4/Smad4 expression and outcome in pancreatic ductal adenocarcinoma. *J Clin Oncol* 2002;20:4531-4542.
32. Salovaara R, Roth S, Loukola A, Launonen V, Sistonen P, Avizienyte E, Kristo P, Järvinen H, Souchelnytskyi S, Sarlomo-Rikala M, Aaltonen LA. Frequent loss of SMAD4/DPC4 protein in colorectal cancers. *Gut* 2002;51:56-59.
33. Bläker H, von Herbay A, Penzel R, Gross S, Otto HF. Genetics of adenocarcinomas of the small intestine: frequent deletions at chromosome 18q and mutations of the SMAD4 gene. *Oncogene* 2002;21:158-164.
34. Planck M, Ericson K, Piotrowska Z, Halvarsson B, Rambech E, Nilbert M. Microsatellite instability and expression of MLH1 and MSH2 in carcinomas of the small intestine. *Cancer* 2003;97:1551-1557.
35. Kuismanen SA, Holmberg MT, Salovaara R, de la Chapelle A, Peltomäki P. Genetic and epigenetic modification of MLH1 accounts for a major share of microsatellite-unstable colorectal cancers. *Am J Pathol* 2000;156:1773-1779.
36. Wheeler JM, Warren BF, Mortensen NJ, Kim HC, Biddolph SC, Elia G, Beck NE, Williams GT, Shepherd NA, Bateman AC, Bodmer WF. An insight into the genetic pathway of adenocarcinoma of the small intestine. *Gut* 2002;50:218-223.
37. Lee MJ, Lee HS, Kim WH, Choi Y, Yang M. Expression of mucins and cytokeratins in primary carcinomas of the digestive system. *Mod Pathol* 2003;16:403-410.
38. Ponz-Sarvisse M, Rodriguez J, Viudez A, Chopitea A, Calvo A, Garcia-Foncillas J, Gil-Bazo I. Epidermal growth factor receptor inhibitors in colorectal cancer treatment: What's new? *World J Gastroenterol* 2007;13:5877-5887.
39. Zhu L, Kim K, Domenico DR, Appert HE, Howard JM. Adenocarcinoma of duodenum and ampulla of Vater: clinicopathology study and expression of p53, c-neu, TGF-alpha, CEA, and EMA. *J Surg Oncol* 1996;61:100-105.
40. Bhargava R, Chen B, Klimstra DS, Saltz LB, Hedvat C, Tang LH, Gerald W, Teruya-Feldstein J, Paty PB, Qin J, Shia J. Comparison of two antibodies for immunohistochemical evaluation of epidermal growth factor receptor expression in colorectal carcinomas, adenomas, and normal mucosa. *Cancer* 2006;106:1857-1862.
41. Playford RJ, Hanby AM, Gschmeissner S, Peiffer LP, Wright NA, McGarrity T. The epidermal growth factor receptor (EGF-R) is present on the basolateral, but not the apical, surface of enterocytes in the human gastrointestinal tract. *Gut* 1996;39:262-266.
42. Zhang MQ, Lin F, Hui P, Chen ZM, Ritter JH, Wang HL. Expression of mucins, SIMA, villin, and CDX2 in small-intestinal adenocarcinoma. *Am J Clin Pathol* 128:808-816, 2007
43. Witek ME, Nielsen K, Walters R, Hyslop T, Palazzo J, Schulz S, Waldman SA. The putative tumor suppressor Cdx2 is overexpressed by human colorectal adenocarcinomas. *Clin Cancer Res* 2005;11:8549-8556.
44. Werling RW, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol* 2003;27:303-310.