CASE REPORT

The coexistence of well-differentiated neuroendocrine carcinoma (carcinoid) of the pancreas and Crohn's disease complicated with systemic AA amyloidosis

A case report

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Abstract. *We describe the case of 75-year-old male with Crohn's disease (lasting 10 years, ileal and colon involvement) where multiple spheric nodules of well-differentiated neuroendocrine carcinoma (carcinoid) in liver parenchyma was proved in July 1999. Although there were both liver lobes involved, carcinoid syndrome occured five years after the diagnosis had been established. Therapy with lanreotide decreased the carcinoid symptoms, not the growth of the tumour mass. To find the origin of the liver metastases the patient underwent intra-operative enteroscopy with following resection of stenoses of distal ileum, ceacum and appendix in February 2005. We did not find the origin of carcinoid metastases of the liver during the patient's life. Crohn's disease was in full-remission the whole time. His health condition was serious and was complicated with bronchopneumonia, which led to death in November 2005. There was well-differentiated neuroendocrine carcinoma of pancreas shown during the autopsy. Another finding during the autopsy was systemic AA amyloidosis as a complication of Crohn's disease.*

Key words: *Crohn's disease, carcinoid, pancreas, carcinoid syndrome, systemic AA amyloidosis*

Pintér M, Papík Z, Kohout A, Vižďa J, Pintérová Kolesárová M, Kopáčová M, Rejchrt S, Bureš J. Současný výskyt diferencovaného neuroendokrinního karcinomu (karcinoidu) pankreatu a Crohnovy choroby komplikované systémovou AA amyloidózou. Kazuistika. Folia Gastroenterol Hepatol 2006; 4 (2): 79 – 85.

Souhrn. *Kazuistika popisuje 75-letého muže s Crohnovou chorobou trvající 10 let s maximem postižení terminálního ilea a céka, u kterého byla v červnu 1999 prokázána vícečetná ložiska dobře diferencovaného neuroendokrinního karcinomu (karcinoidu) v jaterním parenchymu, bez znalosti primárního zdroje. Ačkoliv byly postiženy oba jaterní laloky, karcinoidový syndrom se objevil až po pěti letech od stanovení diagnózy. Léčba lanreotidem snížila příznaky, ale ne velikost nádorových ložisek v jaterním parenchymu. Pro stenózu terminálního ilea a ke zjištění eventuelního primárního zdroje karcinoidu pacient podstoupil v únoru 2005 intraoperační enteroskopii s následnou resekcí terminálního ilea, céka a apendixu. Při této operaci ani v průběhu následujícího období života pacienta jsme však primární zdroj metastáz karcinoidu do jater nenalezli. Crohnova choroba byla po celou dobu v remisi. Pacientův zdravotní stav byl vážný a byl komplikovaný bronchopneumonií, na kterou v listopadu 2005 nemocný zemřel. Při pitvě byl nalezen primární karcinoid pankreatu.*

Klíčová slova: *Crohnova choroba, karcinoid, pankreas, karcinoidový syndrom, systémová AA amyloidóza*

Neuroendocrine tumours (carcinoids) are derived from precursors of endocrine cells of the gastrointestinal tract. They are relatively rare and mostly low-grade malignant. In general, they grow slowly compared with the more frequently occurring and more aggressively growing adenocarcinomas of the gastrointestinal tract. Endocrine tumours are mostly functionally inactive. Some of them, however, could be functionally active and respond with sometimes dramatic clinical syndromes caused by excess hormone release. Metastatic tumours compromise the patient's quality and length of life (1,23). Epidemiological studies of neuroendocrine tumours are scarce and only few risk factors have been suggested, such as tobacco smoking (12,17), cholecystectomy or previous peptic ulcer (12), gallstones (15), and Crohn's disease (3,7,9,18,21,30). The WHO classification has divided the neuroendocrine tumours due to location, tumour differentiation and biological behaviour (1).

The AA amyloidosis is a well-known but relatively rare disease, which may complicate chronic inflammatory diseases, chronic infections, familial Mediterranean fever and occasionally malignant diseases. The studies reported amyloidosis clinically in 0.9 % of patients with Crohn's disease (8).

We describe a case of well-differentiated neuroendocrine carcinoma (carcinoid) of the pancreas with multiple metastases in liver parenchyma in a patient with systemic AA amyloidosis complicating Crohn's disease.

Case report

The patient was a 75-year-old male with Crohn's disease lasting 10 years. Mostly the terminal ileum and caecum were affected. There were multiple stenoses in the distal ileum, including its distal part described during enteroclysis. The patient also suffered from diabetes mellitus type 2 with diabetic

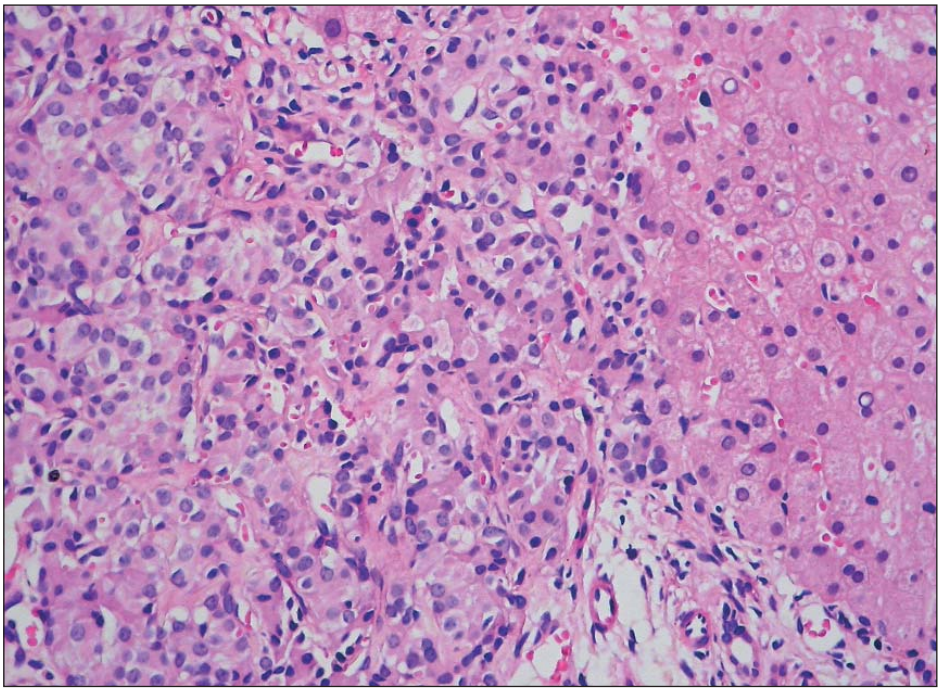


Figure 1
The liver tissue infiltrated by a well-differentiated neuroendocrine carcinoma originated in the pancreas. Haematoxylin-eosin, magnification 200x.

Figure 2
The expression of synaptophysin in carcinoid cells proved immunohistochemically, magnification 200x.

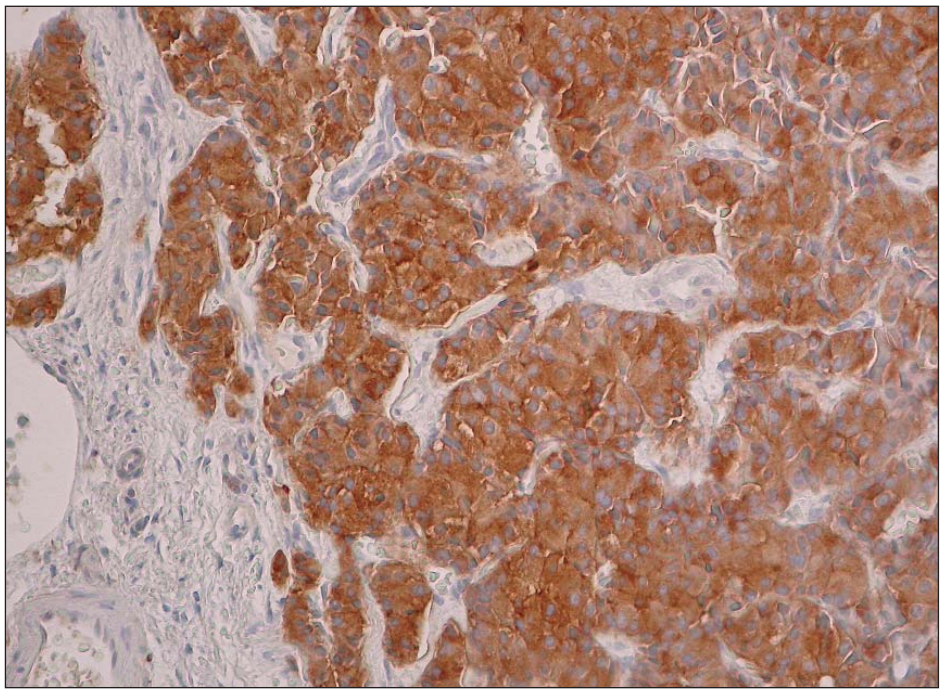
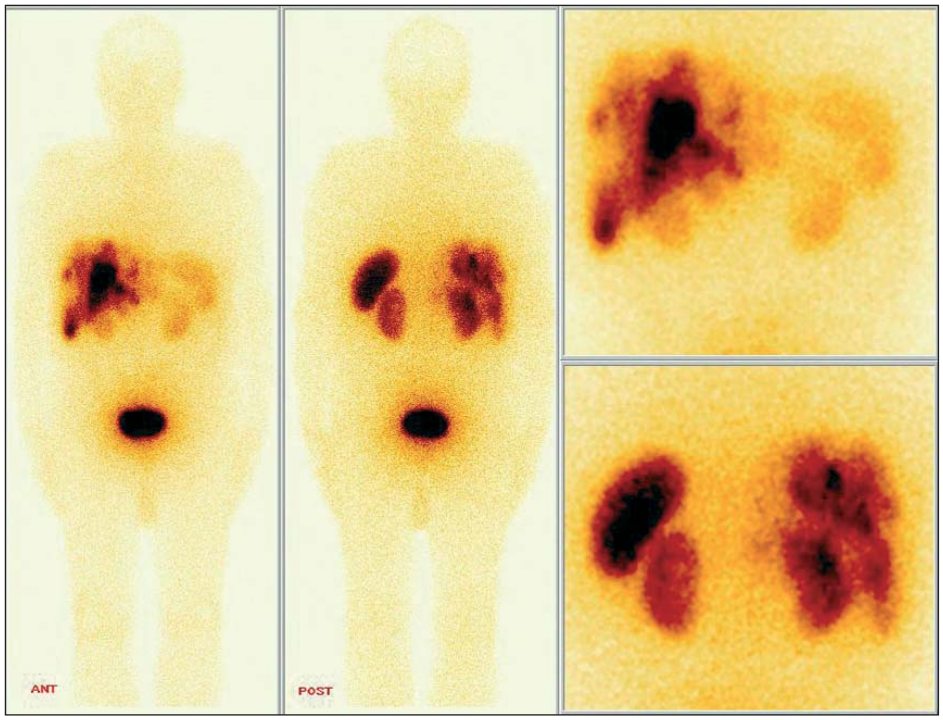


Figure 3
Multiple liver deposits of pathological accumulation of ^{111}In-pentetreotide in tumorous tissue with high concentration of somatostatin receptors. The examination could not exclude the subhepatal origin. ^{111}In-pentetreotide scintigraphy.



nephropathy (proteinuria 0.25 gram per day, selectivity was not determined), non-proliferative diabetic retinopathy, and diabetic distal sensitive neuropathy. The multiple nodules in both lobes of the liver were found in July 1999 leading to liver biopsy. The patient was symptom-free that time, the inflammatory bowel disease was in full remission. He had no history of vomiting, diarrhoea, flush, or any other symptoms before. The tumour was diagnosed initially as a hepatocellular carcinoma, then shown to be a well-differentiated neuroendocrine carcinoma (malignant carcinoid) immunohistochemically staining positive for synaptophysin, chromogranin A and Leu-7 (Figs 1 and 2). To exclude the possibility of metastatic carcinoid tumour from an extrahepatic origin abdominal ultrasound examination, upper gastrointestinal endoscopy and colonoscopy was carried out, no carcinoid tumour was found. The level of 5-hydroxyindoleacetic acid in urine collection was not elevated. Symptomatic therapy was chosen. The patient was admitted to our Department in October 2001 again complaining of weight loss (40 kilogrammes per year),

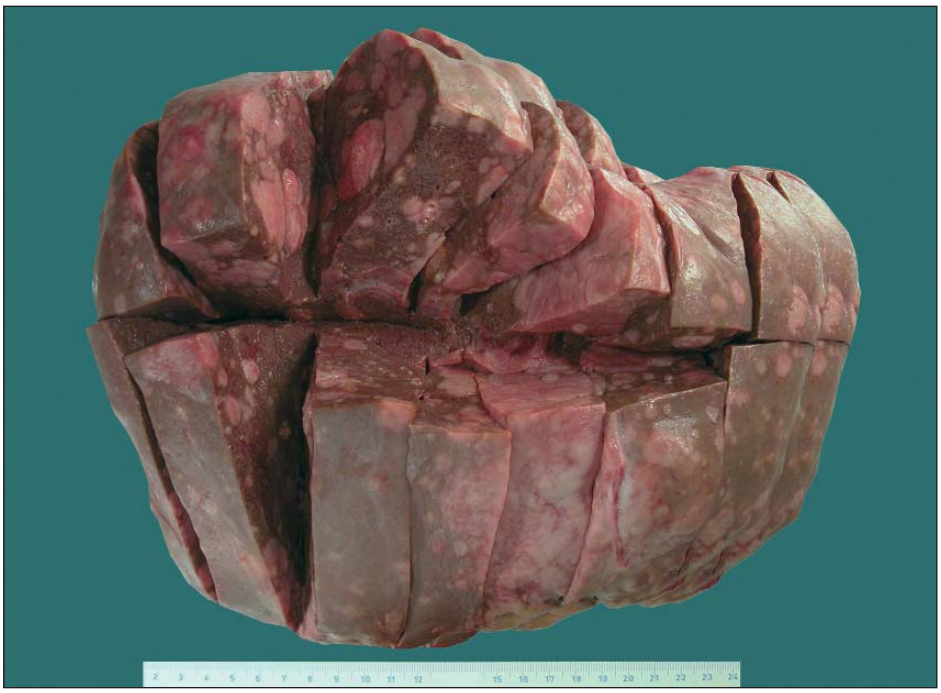


Figure 4
Multiple liver metastases of well-differentiated neuroendocrine carcinoma of the pancreas.

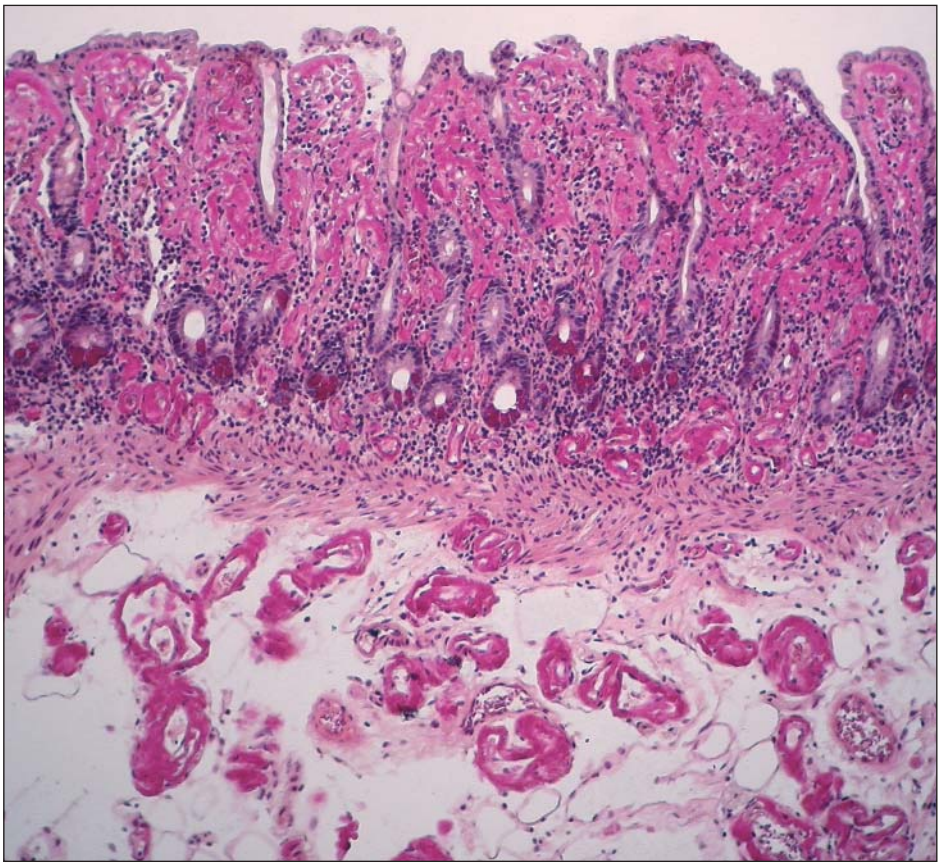


Figure 5
Deposits of AA amyloid in lamina propria mucosae and in the blood vessel walls of duodenal submucosa. Saturn red, magnification 100x.

diarrhoea and tiredness. We repeated the endoscopic examinations, chest and abdominal CT scans and ^{111}In-pentetreotide scans (Fig. 3). Only the Octreoscan could not exclude the tumour mass in subhepatal area (the edge of the liver was not sharp), but the abdominal CT scans were negative. Therapy using somatostatin analogue lanreotide (90 mg per month) has been administrated with good response since that time, controlled regularly. Since October 2001 once the flush had been present. He was admitted again in February 2005 due to anasarca with good response to diuretic therapy. A control colonoscopy and enteroclysis were carried out. There were multiple stenoses in the distal 75 cm part of the ileum with

4 – 15 mm diameter. The small bowel relief was smoothed and rigid during enteroclysis. To find the primary site of carcinoid tumour we decided to make the intra-operative enteroscopy with following resection of stenoses of distal ileum, ceacum and appendix in February 2005. There was only endoscopic view of inflammatory involvement with stenoses of the distal ileum. The resection of 38 cm of terminal ileum, appendix and caecum with a side-to-side anastomosis was carried out. Histology revealed crypt architectural abnormalities, severe chronic inflammation, no carcinoid tumour was found. Last admission for weight loss (8 kilogrammes per 6 months) and diarrhoea was in October 2005. There was a progression of growth of the tumour mass in the liver according to ultrasound examination. His health condition was serious and was complicated with bronchopneumonia which led to his death in November 2005. The autopsy found a 2-cm nodule in the pancreatic tissue, histologically consisting of small cells with granular chromatin, stained positively for synaptophysin, chromogranin and Leu-7, identical with the liver metastases (Fig. 4). Another finding in the post-mortem examination was secondary amyloidosis of the oesophagus, intestine (Fig. 5), liver, spleen, adrenal glands and kidneys.

Discussion

We describe the case of 75-year-old male with Crohn's disease (lasting 10 years) where multiple spherical nodules of well-differentiated endocrine carcinoma (carcinoid) in liver parenchyma were proved. There was well-differentiated neuroendocrine carcinoma of the pancreas shown during the autopsy as a primary tumour.

Carcinoid has been found to originate in almost every organ derived from the primitive endoderm. Modlin & Sanborn's epidemiological study of 13,715 cases indicated that 67.5 % occur in the gastrointestinal tract, the tracheobronchial site being the second most common with 25.3 %. Within the gastrointestinal tract, the majority occurred in the small bowel (41.8 %), appendix (12.2 %), rectum (27.4 %) and stomach (8.7 %). Neuroendocrine carcinomas of the pancreas are very rare, only 79 cases (0.73 %) have been described since 1973. At the time of diagnosis, 72 – 81 % of patients had non-localized disease and the overall 5-year survival rate was only 37.5 % (22). Carcinoid tumour has been also found in such unusual locations as the oesophagus, bile duct, ampulla of Vater, Meckel's diverticulum (19) and as a primary hepatic carcinoid (2,13,14). The pancreatic carcinoid exhibited a high metastatic rate (66.7 %) and revealed a relatively high frequency of the carcinoid syndrome (23.3 %) (24). The five-year survival rate is extremely low (28.9 ± 16.7 %) in Soga's analysis (29). There were 1,314 carcinoid tumours registered in the period 1984 – 1994 in the Czech National Oncology Register. A total of 987 carcinoids (75 %) occurred in the gastrointestinal tract, mostly in the large bowel (appendix, colon, rectum, 44 %), and in the small bowel (26 %). Thirty-one carcinoids occurred in pancreas (2.4 %) which is more than in Modlin's study (31). The primary extrahepatic carcinoid tumour metastases in the liver and often not beyond the liver. Apart from the liver, the next most frequent site of distant metastases is skeleton, and very rarely the female breast and ovary (19). To exclude the possibility of metastatic carcinoid tumour from an extrahepatic origin, intensive examinations including upper gastrointestinal endoscopy, intra-operative entero-scopy, colonoscopy, abdominal and chest CT scans and the ^{111}In-pentetreotide scan were carried out in our patient. Only the Octreoscan could not exclude the tumour mass in subhepatal area (the edge of the liver was not sharp), but the abdominal CT scans were negative. We did not confirm any other metastases, only the liver. The presence of liver carcinoid (as a rare primary hepatic carcinoid tumour or more often metastases of the carcinoid tumour) usually means carcinoid syndrome but only when serotonin is produced. This syndrome is characterized by flush, diarrhoea, and less commonly, wheezing, heart-valve dysfunction, and pellagra (5). The symptoms result from the synergistic interaction between 5-hydroxytryptamine metabolites, kinins, and prostaglandins released by the tumour into the general circulation. The 5-hydroxyindoleacetic acid levels in 24-hour urine collections are usually high (5). The carcinoid involvement of the patient's liver was finally more than 70 %, but the level of 5-hydroxyindoleacetic acid in urine collection was repeatedly not elevated. Carcinoid syndrome was present. The patient suffered from diarrhoea and episodes of flush. Surgical removal was not possible from the beginning since there were multiple tumour foci affecting both lobes of the liver. The therapy with inhibitors of 5-hydroxytryptamine release – lanreotide was adminis-

trated since the symptoms of carcinoid had occurred. Lanreotide is a somatostatin analogue with slow-release formulation and has been shown to be effective in controlling symptoms and may have some anti-tumour activity (28). The symptoms in our case were reduced using lanreotide, but not the extent of the tumour.

Another finding was the systemic AA amyloidosis as a complication of Crohn's disease. The gastrointestinal tract, liver, spleen, adrenal glands and kidneys were involved. The AA amyloidosis is a well-known but relatively rare disorder which may complicate inflammatory bowel disease. The studies reported amyloidosis clinically in 0.9 % of patients with Crohn's disease (8).

The chief sites of intestinal amyloid deposition are blood vessel walls (producing ischaemia and infarction), the muscle layers of the intestine (causing dysmotility), and the lamina propria mucosae (impairing absorption) (31). That is the reason why the AA amyloidosis can also mimic Crohn's disease (26). The diagnosis of amyloidosis is made by appropriate histology demonstrating Congo red positive amyloid deposits on fat-pad biopsy duodenal, rectal or renal biopsy (6,10). In patients with Crohn's disease and AA amyloidosis, proteinuria is the most common symptom (8,16,32), however, many other symptoms in the literature are connected with the involvement of the liver, the thyroid gland etc (11,27). The overall 5-year lethality for AA amyloidosis is 50 % (5,20). There is no correlation with suppurative complications or with the extent or duration of inflammatory bowel disease in most studies (cited in 25), but in other reports, 70 % of patients had suppurative complications and extraintestinal manifestations (8,32). We did not prove any suppurative complications nor extraintestinal manifestations of Crohn's disease in our patient. In patients with Crohn's disease and AA amyloidosis, proteinuria is the most common presentation (8,16,32) and nephropathy is the most common lethal disorder of inflammatory bowel disease-associated amyloidosis (4). The patient in our case report suffered from diabetes mellitus type 2 with diabetic nephropathy with 0.25 gram of proteinuria per day (selectivity was not determined). The proteinuria was assigned to diabetic nephropathy. The structure of the kidneys was normal during ultrasound examinations and proteinuria was too low to accuse the amyloidosis.

Well-differentiated neuroendocrine carcinoma (carcinoid) of the pancreas is rare and there is no report of an association with Crohn's disease. We describe a case of primary carcinoid tumour in the pancreas with multiple liver metastases in a patient with secondary amyloidosis complicating Crohn's disease.

REFERENCES

1. Arnold R. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. Best Pract Res Clin Gastroenterol 2005; 19: 491-505.
2. Asakawa T, Tomioka T, Abe K, Yamaguchi T, Tsunoda T, Kanematsu T. Primary hepatic carcinoid tumor. J Gastroenterol 1999; 34: 123-127.
3. Auber F, Gambiez K, Desreumaux P, Mudry J, Lecomte-Houcke M, Cortot A, Quandalle P, Colombel JF. Mixed adenocarcinoid tumor and Crohn's disease. J Clin Gastroenterol 1998; 26: 353-354.
4. Becker SA, Bass D, Nissim F. Crohn's ileitis complicated by amyloidosis: observations and therapeutic considerations. J Clin Gastroenterol 1985; 7: 296- 300.
5. Caplin ME, Buscombe JR, Hilson AJ, Watkinson AF, Burroughs AK. Carcinoid tumour. Lancet 1998; 352: 799-805.
6. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997; 337: 898-899.
7. Freeman HJ. Appendiceal carcinoids in Crohn's disease. Can J Gastroenterol 2003; 17: 43-46.
8. Greenstein AJ, Balasubramanian S, Harpaz N, Rizwan M, Sachar DB. Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. Am J Gastroenterol 1997; 92: 682-685.
9. Greenstein AJ, Sachar DB, Panday AK. Amyloidosis and inflammatory bowel disease. A 50-year experience with 25 patients. Medicine 1992; 71: 261-270.
10. Gries E, Singer MV, Goebell H. Amyloidosis in Crohn disease. Case reports and review of the literature. Med Klin (Munich) 1989; 84: 65-71.
11. Habu S, Watanobe H, Kimura K, Suda T. A case of amyloid goiter secondary to Crohn's disease. Endocrinol J 1999; 46: 179-182.
12. Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev 1994; 3: 205-207.
13. Iimuro Y, Deguchi Y, Ueda Y, Tanaka A, Iwasa Y, Ishihara M, Mizuta K, Yamamoto Y, Ikai I, Shimahara Y, Yamaoka Y. Primary hepatic carcinoid tumor with metachronous lymph node metastasis after long-term follow up. J Gastroenterol Hepatol 2002; 17: 1119-1124.
14. Iwao M, Nakamuta M, Enjoji M, Kubo H, Fukutomi T, Tanabe Y, Nishi H, Taguchi K, Kotoh K, Nawata H. Primary hepatic carcinoid tumor: case report and review of 53 cases. Med Sci Monit 2001; 7: 746-750.
15. Johansen C, Chow WH, Jorgensen T, Mellemkjaer L, Engholm G, Olsen JH. Risk of colorectal cancer and other cancers in patients with gall stones. Gut 1996; 39: 439-443.
16. Joss N, McLaughlin K, Simpson K, Boulton-Jones JM. Presentation, survival and prognosis markers in AA amyloidosis. Q J Med 2000; 93: 535-542.
17. Kaerlev L, Teglbjaerg PS, Sabroe S, Kolstad HA, Ahrens W, Eriksson M, Guenel P, Gorini G, Hardell L, Cyr D, Zambon P, Stang A, Oljen J. The importance of smoking and medical history for development of small bowel carcinoid tumor: a European population-based case-control study. Cancer Causes Control 2002; 13: 27-34.
18. Kulkarni D, Pinto DJ. Coexistence of Crohn's disease and neuroendocrine tumour of appendix: more than coincidence? Int J Pract 2005; 59: 852-853.

19. Kvols LK. Gastrointestinal Carcinoid Tumors and the Malignant Carcinoid Syndrome (p 1831-1843). In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, ed 6th Ed. Philadelphia: Saunders, 1998.
20. Lovat LB, Madhoo S, Pepys MB, Hawkins PN. Long-term survival in systemic amyloid A amyloidosis complicating Crohn's disease. Gastroenterology 1997; 112: 1362-1365.
21. Mellemkjaer L, Johansen C, Gridley G, Linet MS, Kjaer SK, Olsen JH. Crohn's disease and cancer risk (Denmark). Cancer Causes Control 2000; 11: 145-150.
22. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97: 934-959.
23. Mullan MH, Gauger PG, Thompson NW. Endocrine tumours of the pancreas: review and recent advances. J Surg 2001; 71: 475-482.
24. Onaitis MW, Kirshbom PM, Hayward TZ. Gastrointestinal carcinoids, characterization by site of origin and hormone production. Ann Surg 2000; 232: 549-556.
25. Pardi DS, Tremaine WJ, Sanborn WJ, McCarthy JT. Renal and urologic complications of inflammatory bowel disease. Am J Gastroenterol 1998; 93: 504-514.
26. Parente F, Miteni M, Anderloni A, Lazzaroni M, Porro GB, Danelli PG, Sampietro G, Zerbi P. Carcinoid mimicking ileal Crohn's disease. Gastrointest Endosc 2005; 61: 105-106.
27. Rusynyk AR, Ghosh MS, Varano VJ, Grundfast MB. Secondary amyloidosis of the liver as the primary manifestation of Crohn's disease. Am J Gastroenterol 2002; 97, Suppl 488: S161.
28. Ruszniewski P, Ducreux M, Chayvialle JA. Treatment of the carcinoid syndrome with the long acting somatostatin analogue lanreotide: a prospective study in 39 patients. Gut 1996; 39: 279-283.
29. Soga J. Carcinoid of the Pancreas. Cancer 2005; 104: 1180-1187.
30. Szabo GG, Barta Z, Kerekes L, Szakall S. Association of carcinoid tumor of the appendix and Crohn's disease (case report and review of literature) (in Hungarian). Orv Hetil 1999; 140: 1635-1639.
31. The National Oncology Register of the Czech Republic. Carcinoids in period 1984 – 1994. Praha: ÚZIS, 1998.
32. Weber JR, Ryan JC. Effects on the gut of systemic disease and other extraintestinal conditions (p 411-438). In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 6th Ed. Philadelphia: Saunders, 1998.
33. Wester AL, Vatn MH, Fausa O. Secondary amyloidosis in inflammatory bowel disease: A study of 18 patients admitted to Rikshospitalet University Hospital, Oslo, from 1962-1998. Inflamm Bowel Dis 2001; 7: 295-300.

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