Colorectal carcinoma and polyposis

Štěpán Hlava
Interní klinika FN v Motole

Epidemiology

- Lifestyle disease
- Incidence is higher in developed countries
- Czech Republic has long term the highest incidence
  - 75 for 100 000 people (1999)
  - 6300 death per year
- Half of tumors diagnosed in advanced stadium
- Higher incidence in male
- Close relatives are in higer risk (3-4x)
- Incidence increases with age

Pathogenesis

- Genetic factors
- Environmental factors
- 2 widely acclaimed theories
  - Formation from adenoma polyp
    - Hyperprolyferative mucosa
    - Adenoma
    - dysplastic cells
      - low grade, high grade
    - carcinoma in situ
    - invasiv carcinoma

Pathogenesis

- Formation de novo
  - Without presence of polyps
  - Allredy small tumors invade to deep lyers or have metastases
  - More agresive
  - Histologicaly sharp transition from carcinoma to heathy mucosa

Etiology – environmental factors

- Smoking
- Beer – (adenocarcinoma of rektum)
- Faty meat
- Red meat
- Grilled and smoked food
- Alcohol
- Disbalance in income and outcome of energy
- Low level of vitamine D

Etiology – genetic factors

- Oncogene activation
- Tumor supressor gene inactivation
- APC gene
- Activation of K-ras (5.chromosome)
- P53 tumor supressor gen inactivation
- ras, src, c-myc, c-erbB-2
- The failure of the repair process (microsatelite instability - Lynch syndrom)

Primary prevencion

- The high fiber content in food
- Low content of animal fat
- Ideal weight
- Enaugh excercise
- Aspirin ?

Secundary prevention

- Screening program
- Early colonoscopic detection
- Endoscopic polyps removal
- Detection of carcinoma in early stadium (possible radical ressection)

Precancerosis

- Lesions on the basis of which frequently arises carcinoma
  - Adenoma polypes
- Pathological units associated with a higher incidence of colorectal cancer
  - Polyposis,Lynch syndrom
  - Ulcerative colitis
  - Patient post polypectomy, post resection of colorectal cancer
  - ureterosigmoideoanastomosis

Clinical presentation

- Symptoms are initially mild
- Symptoms are determined by tumor localization and size
- Narrowing of the intestine lumen
  - Lower dyspeptic syndrom
  - Defecation stereotype change
  - Subileus, ileus
- Tumor exulceration
  - Microscopic/macroscopic bleeding

Clinical presentation

- Anemia, anemic syndrom
- Perforation, peritonitis (rare)
- Penetration into the surroundings, palpable mass
- Manifestations of metatsatic spreading (lung, liver, ovaries, peritoneum)
- Cachexia, weight loss, fatigue…
- according localization:
  - Right colon – weight loss, anemia
  - Left colon – bleeding, subileus,ileus, defecation stereotype change (alternating diarrhea-constipation)
  - Rectum - tenesmus

Examination methods

- Medical history, physical examination with per rectum
- Test for ocult bleeding
- **Endoscopy and biopsy**
- EUS (rectum)
- CT colography
- USG of abdomen
- CT of abdomen, lung
- Chest X-ray
- MRI of pelvis(rectal cancer)
- Biochemistry, hematology
- Oncomarkers: CEA, CA 19-9

Classification

- By location
  - Rectum(40-60%)
  - Left side / right side
  - Synchronous, metachronous (about 6%)
- Endoscopic classification (according to appearance)
  - Polypous, ulcerative, flat (ulcerated),infiltativ
  - Linitis plastica – high fibroproduction, wall induration

Classification

- Microscopic classification
  - Adenocarcinoma
    - tubulous
    - Different degree of differentioation
  - Carcinoi (1%)
  - Lymfoma (0,2%)
  - Sarkoma (0,1%)
  - Spinocelular carcinoma, basalioma, melanoma

Staging

- Extent of the disease
- TNM klassification (tumor, lymf nodes, metastasis)
- Stadium I-IV

Stage	Level of involvement
Tumor	
T1	Limited to mucosa and submucosa
T2	Extension into but not through muscularis propria
T3	Invasion of perirectal fat
T4	Invasion of adjacent structures
Nodes	
N0	No involved lymph nodes
N1	Fewer than four regional nodes involved
N2	More than four regional nodes involved
N3	Distant nodes involved
Metastasis	
M0	No metastasis
M1	Distant metastasis

Grading

- The degree of tumor differentiation
  - differentiated
  - moderately differentiated
  - low differentiated(anaplastic)

- Agresivity, prognosis

Therapy

- Therapeutic modalities
  - Radical resection
  - Paliativ surgery, resection of solitry metestases
  - Endoscopic paliatic treatement (stents)
  - Systemic chemotherapy – neoadjuvant, adjuvant
    - 5-fluoruracil, oxaliplatina,leukovorin, irinotekan kapecitabin
  - Locál chemotherapy of liver metastasis, embolization, hyperthermic destruction

Therapy

- Radiotherapy (rectum)
- Systemic palliative therapy
- Biologic therapy
  - Bevacizumab (Avsatin) vascular growth factor inhibitor
  - Cetuximab (Erbitux) epidermal growth factor inhibitor

Therapy

- TNM 0-I. (mucosa, submucosa)
  - polypectomy(TNM 0), wide excision
- II, III.(wall, regional lymph nodes)
  - Neoadjuvant chemotherapy
  - Wide excision
  - Adjuvant chemotherapy
  - Neoadjuvant radiotherapy (rectum)
- IV.(distant metastases)
  - Systemic palliative chemotherapy, biological therapy

Therapy

- Supportive therapy!!!
  - Antiemetics (setrons)
  - Effective treatment of pain
  - Blood transfusions
  - Psychological support

Prognosis

- Five-year survival
  - TNM 0-I 80-90%
  - TNM II (60-80%)
  - TNM III 50-60%

Colonic polyps

- Hyperplastic polyps
  - Without dysplastic changes
  - The most commonly in the rectosigmoid,
  - Most often to 5 mm in size
  - Very little risk of malignancy
  - Increased risk with larger and more proximal growing
- Adenoma serratum
  - Hyperplastic polyp with adenoma tissue
  - Dysplastic changes, the risk of malignant transformation
- Inflammatory pseudopolyps (IBD)

Colonic adenomas

- Dysplastic changes
- Synchronous, metachronous
- Tubular structure – 80%
- Vilous structure – elongated glands 10-15%, the risk of metachronous adenomas is higher
- Tubulovilous adenoma
- Malignization risk:
  - Size, histology (villous component)
  - Grade of dysplasia (Vienna classification)
  - Number of polyps

Familiar adenomatose polyposis (FAP)

- AD disease
- APC gen mutation
- TS gen – chromosome 5
- It encodes a large protein beta catenin
- Role in cell adhesion, communication

Familiar adenomatose polyposis (FAP)

- Over 300 known mutations
- numerous adenoma polyps - more than 100
- Rectum always affected
- Prevalence 1:10 000
- It causes 1% of CRC
- Poylps in 2nd decade
- CRC before the 4th decade

Familiar adenomatose polyposis (FAP)

- Can affect the entire digestive tract
- extraintestinal Symptoms
- The combination of FAP with extra-intestinal symptomatology (mainly osteoma) - Gardner's syndrome
- The combination of FAP brain tumor - Turcottův syndrome
- Congenital hypertrophy of the retinal pigment epithelium
- osteoma
- hyperostosis of the skull and jaws

Familiar adenomatose polyposis (FAP)

- dental anomalies
- impacted / supernumerary teeth, odontogenic cysts
- Epidermoid cysts, fibromas, lipomas
- Polypous changes in the oral part of the digestive tract
- Adenoma of the duodenum and the papilla of Vater
- Small bowel disease
- Benign gastric poylposis - cystic dilatation of the corporal glands
- Adrenal adenomas and carcinomas
- Brain tumors (gliblastom, medulloblastoma, astrocytoma)

AFAP (atenuated FAP)

- Flat , less numerous poyps
- small
- The emergence of cancer later
- Not present retinal hyperpigmentation

Familiar adenomatose polyposis

- Therapy
  - Dispenzary
  - Colectomy
    - Total + pouch
    - Subtotal s with ileo-rekctal anastomosis

HNPCC – Hereditary nonpolyposis colorectal cancer

- AD
- 5% of all CRC
- MMR mismatch gen mutation, mikrosatelite instability (gen MSH2, MLH1, PMS 1 a 2)
- Lower amount of polyps, high risk of malignization
- Lynch 1 – CRC
- Lynch 2 –brest, endometrium, pancreras, stomach, skin, urine bladder

Peutzův Jeghers syndrom

- AD syndrom
- TS genu mutation
- Numerous harmatomas
  - Normal epitelium, branched strips of smooth muscle
  - Mukokutal melanin pigmentation
- Buccal mucosa, lips, nose wings, eyes, hands, anogenital region

Peutzův Jeghers syndrom

- obstruction
- intussusception
- chronic anaemization
- Acute gastrointestinal bleeding
- rare malignancy

Juvenil polyposis

- AD disease
- "Juvenile" fibrous tissue
- Histologically fibrous stroma with inflammatory infiltration, cystic glands dialtované
- It's not precancerosis, but some polyps may contain adenomas
- Most often pedunculated polyps
- 5+
- Frequently rectosigma

Cowden syndrom

- AD
- multiple hamartomas
- Cutaneous, mucosal abnormalities
- Cysts and adenomas of thyroid gland
- Ovarian cyst, uterine fibroids

Syndrom Cronkhite Canada

- V.s. autoimune disease
- Multiple poylps throughout the GIT
- hyperplastic polyps
- Abdominal pain, malabsorption, related weight loss
- Alopecia, dystrphyc nails, neurological disorders
- extremely rare

Cancer screening

- Rules of screening programs
  - treatable disease
  - Cheap, affordable diagnostic method
  - good sensitivity
  - A few false positives
  - Analysis of the cost / yield / profit
  - Patients compliance
  - Reduction in mortality

Screening - goals

- Detection of early stages of CRC
- Detection of precancerous lesions
- Reduction of mortality and morbidity
- Reducing the number of palliative patients treated
- Reducing the need for further cancer treatment

Screening program for colorectal cancer in the Czech Republic

- asymptomatic patient
- Age over 50 years
- Negative family history
- Every year occult blood test
  - (practitioner, gynecologist)
  - Guaiac tests (psudoperoxidase reaction)
  - immunohistochemical tests
- When positivity colonoscopy

Screening program for colorectal cancer in the Czech Republic

- 55 years up possibility of choice
- Occult blood test every 2 years
  - When positivity colonoscopy
- Primary screening colonoscopy
  - negative finding - another colonoscopy every 10 years
  - Positive findings - follow-up
- Nondiagnostic colonoscopy (preparation, algic response ...)
- repeated in better conditions
- Choose another method (CT colonography, colonoscopy, capsule)

The screening program - difficulties

- Relatively little compliance
- Addressable inviting
- Quality of colonoscopy / Preparation
- screening centers
- dispensary

Dispensary programs

- Should be distinguished from screening
- High-risk patients
- Follow-up after the polypectomy, resections

Dispensary programs

- Intestinal polyposis
- FAP, Gardner's syndrome, Turcot syndrome
  - 10-12 years of age sigmoidoscopy and 1 year
  - If you find polyposis consider colectomy

Dispensary programs

- Lynch I, II
  - Identification of individuals at risk on the basis of the Amsterdam criteria
- Amsterdam criteria
  - at least three relatives with colorectal cancer
  - two consecutive generations
  - At least one of the affected under 50 years
  - Due to family size criteria are too strict
- Total colonoscopy from 20 to 30 years, every 1-2 years
- From 40 years of age annually
- genetic testing

Dispensary programs

- Relatives 1st level of patients with CRC
  - FOBT since 40 years
- Patients after polypectomy of adenomas
  - Decides grade of dysplastic changes
  - Polyp size, the number of polyps
  - In carcinoma in situ is necessery have s safe rim of healthy tissue (Morsons criteria)

Dispensary programs

- Patients with IBD
- Ulcerative colitis + m.Crohn with colonic disease
- Left form colonoscopy after 15 years of disease
- Complete form of colonoscopy after 8 years of disease
- 1-2 years follow up
- Primary sclerosing cholangitis
- Sets of biopsies, chromoendoscopy

Conclusion

- Incidence of colorectal cancer in the Czech Republic is high
- Often capture at an advanced stage
- Histologically prevails adenocarcinoma
- Development hyperproliferative mucosa-adenoma-carcinoma
- Secondary prevention - screening program