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Inflammatory bowel disease and gastrointestinal malignancies – risks, incidence and management

Idiopatické střevní záněty a gastrointestinální malignity – rizika, incidence a management

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Summary: Inflammatory bowel disease (IBD) is characterized as an immunomediated chronic inflammation in Crohn's disease and ulcerative colitis. Although the exact cause of IBD is not entirely clear, an abnormal reaction of the immune system towards physiological microbiota in the colon and small bowel is suspected. IBD has long been associated with an increased risk of malignancies. The main risk is IBD-associated colorectal cancer, which is caused by chronic inflammation, followed by other cancers (including extraintestinal cancers) that develop as a result of the inflammation and subsequent treatment with immunosuppressors/ /biologics. Recent advances in immunosuppressive therapies have significantly improved prognosis as well as quality of life of IBD patients. However, longer survival means prolonged exposure to chronic inflammation as well as to immunosupression (biologics), which translates into a higher risk of cancer development. Therefore, in addition to anti-inflammatory therapies, current strategies for the management of IBD patients also include cancer prevention and surgery, systemic therapy, radiotherapy, and hormonal therapy. The current paper describes the major risk factors of malignancy in IBD patients, and provides an overview of the most commonly occurring IBD-associated gastrointestinal cancers and their management.

Key words: inflammatory bowel disease – neoplasms – primary sclerosing cholangitis – risk

Souhrn: Idiopatické střevní záněty (IBD – inflammatory bowel disease) představují imunitně zprostředkovaná chronická zánětlivá onemocnění mezi která řadíme Crohnovu nemoc a ulcerózní kolitidu. Jejich přesná příčina není známa, avšak vychází z hypotézy abnormální reakce imunitního systému u geneticky vnímavých jedinců. Imunitní systém chybně rozpoznává fyziologické mikrobioty v tlustém a tenkém střevě a nesprávně je interpretuje jako patogeny. U IBD je znám vyšší výskyt maligních nádorů trávicí trubice, především kolorektálního karcinomu, kde hlavním rizikovým faktorem je chronický zánět, ale také nádorů extraintestinálních, které vznikají nejen následkem chronického zánětu, ale/nebo i v důsledku imunosupresivní/biologické léčby. Pacienti s IBD se díky pokroku v léčbě imunosupresivy a především biologiky dožívají vyššího věku. Současně s tím se však prodlužuje délka trvání chronického zánětu a expozice imunosupresivům/biologikům a zároveň tak stoupá riziko vzniku malignity. Pacienti s IBD tak mimo základní protizánětlivé léčby vyžadují i léčbu onkologickou zahrnující chirurgii, chemoterapii, radioterapii nebo léčbu hormonální. Článek je zaměřen na charakteristiku rizikových faktorů maligních nádorů u pacientů s IBD, jejich výskyt a management.

Klíčová slova: idiopatický střevní zánět – nádor – primární sklerozující cholangitida – riziko

Introduction

IBD-associated malignant tumors can be categorized by mechanisms of their initiation as 1. caused by the exposure to chronic inflammation, 2. resulting from the effects of immunosuppressive IBD therapy or 3. arising due to other causes. The most prominent first group includes IBD-associated colorectal cancer (IBD-CRC), small bowel adenocarcinoma, anal carcinoma and cholangiocarcinoma. The therapy-related malignancies include lymphoproliferative disorders such as non-Hodgkin's lymphomas and leukemia, malignant melanoma as well as non-melanoma skin cancer (NMSC), cervical cancer and certain types of

oral cancers. Finally, the last group of IBD-associated cancers of unknown or uncertain cause includes prostate, lung and bladder cancer in men and breast and lung cancers in women [1].

IBD-CRC

Identified in the 1920s by the early works of Crohn, Rosenberg et al. [2,3], IBD-CRC is the most common malignancy in IBD patients arising directly as a result of colonic tissue exposure to chronic inflammation. The risk increases with IBD duration, extent and activity and it is further elevated by coexisting primary sclerosing cholangitis (PSC) as well as family history of colorectal cancer. The onset of IBD-CRC is generally 10–15 years earlier compared to sporadic colorectal cancer. It is therefore common in younger patients, typically in proximal colon with mucinous histology. Also, two or more synchronous lesions are frequently found [4]. The early onset of IBD is often thought to be a potential independent risk factor for IBD-CRC, however recent meta-analyses did not support such an assumption. There is, on the other hand, a direct risk association with the duration of the IBD. In the case of Crohn's disease (CD) the cumulative risk is 2.9% at 10, 5.6% at 20 and 8.3% at 30 years of the disease duration [5]. The IBD-CRC risk for ulcerative colitis (UC) is 2% at 10, 8% at 20 and an alarming 18% at 30 years of disease duration [6,7]. Furthermore, studies have clearly documented an association of the malignancies with the extent of the IBD disease. The relative risk compared to the general population is 1.7 for proctitis, 2.8 for left-sided colitis and 14.8 for pancolitis [4]. Furthermore, the severity of inflammation assessed by colonoscopy with subsequent histology evaluation is directly correlated to the risk of neoplasia [4]. Most importantly, mucosal healing was found to reduce the risk of IBD-CRC to the levels of the average risk of sporadic colorectal cancer in the general population.

Gender and family history have also both been recognized to contribute as independent IBD-CRC risk factors. The relative risk for men is 2.6, 1.9 for women, while a cumulative incidence at 40 years of disease duration is 8.3 and 3.5 for men and women, resp. [4]. In a family with a history of sporadic colorectal cancer the risk of IBD-CRC is 2–3 fold higher.

Finally, a coexisting PSC, a chronic cholestatic disease of the liver, presents a significant risk for the development of malignancy in IBD patients [8]. It is less frequent in CD (10%) compared to UC (up to 80%). At the same time, PSC incidence depends on the extent of the disease with 1% for distal colitis and 6% for pancolitis. PSC has clearly been linked to IBD-CRC in a meta-analysis of 11 studies totaling 168,444 IBD patients. From a subgroup with concomitant IBD and PSC a total of 21% with developed cancer, while only 4% of patients without PSC [9]. In the long-term assessment, the incidence of IBD-associated colorectal cancer has been steadily decreasing. This could be attributed to the ongoing improvement in IBD therapy by a new generation of immunomodulators and biological agents that efficiently support the mucosal healing, thus reducing the exposure-mediated IBD-CRC initiation [5].

Pathogenesis and incidence

Molecular mechanisms of IBD-CRC initiation and progression were proposed in 2009 [10] as an alternative to the classic Vogelstein model of sporadic colorectal neoplasia [11]. In both cases the pathogenesis is fundamentally outlined by morphological changes during the adenoma–carcinoma sequence. Although similar molecular pathways and associated genetic aberrations (point mutations, allelic deletions, hypermethylation, etc.) are involved in IBD-associated as well as sporadic CRC, there is a characteristic difference in timing and sequence of the events. In IBD-CRC inactivation of tumor suppressor TP53 represents an early event affecting mucosa followed by microsatellite instability and chromosomal instability underlying low-grade dysplasia (LGD) and mutations in *KRAS* and *APC* leading to carcinoma [12]. Hence the process is a reversed sequence of sporadic colorectal carcinogenesis which is typically faster and multifocal [13]. The initiation of colonic neoplasia through TP53 somatic mutations is a result of ongoing oxidative and nitrosative stress within mucosa undergoing inflammatory response [14]. The neoplasia is further supported by the interaction of immune cells, epithelial cells and stroma through inflammatory mediators, including tumor necrosis factor alpha (TNF-α) and a family of cytokines (IL-1, IL-6, IL-12, IL-13, IL-17, IL-22 and IL-23) [15]. Recent studies support the importance of gut microbiota in the IBD-CRC pathogenesis. In particular, the intestinal microbiome interactions with the host genome of the colonic epithelial cells is key in the development of cancer [13,16].

Management

Prevention of IBD-CRC is fundamentally based on colonoscopy surveillance [17], which is deeply reliant on close collaboration with patient, bowel preparation, precise biopsies, and the ability of the endoscopist to accurately recognise dysplastic lesions. Such surveillance is often challenging due to a presence of inflammation or inflammatory polyps. Dysplastic lesions in IBD are often flat without demarcated borders and therefore difficult to detect under normal white light. Therefore, new techniques such as high-resolution endoscopy and chromoendoscopy with targeted biopsies improve the overall detection rates [18]. Despite the current absence of randomized control

studies, the surveillance colonoscopies are currently recommended as best practice by all major societies, including American Gastroenterological Association, American Society for Gastrointestinal Endoscopy and European Society for Gastrointestinal Endoscopy [19].

According to the original guidelines, surveillance should be started at 8 to 10 years from the IBD onset in the case of pancolitis, 15 years from onset in the case of left-sided colitis. However, more recent studies have unveiled an uncovered carcinoma in 17–35% of patients mainly due to the late start of the surveillance program [20]. The current recommendations are therefore based on entry colonoscopy 8 years from the IBD onset (UC, pancolitis, left-sided colitis or CD affecting more than 1/3 of the colon).

The intervals of surveillance colonoscopy are determined by the individual risk. In high-risk patients (i.e. those with stenosis, high-grade dysplasia (HGD) or LGD, coexisting PSC, extensive colitis with severe inflammation or patients with a positive family history of CRC in a first-degree relative before 50 years of age), the recommendation is for a 1-year interval. In patients at intermediate risk (extensive colitis with mild or moderate active inflammation, postinflammatory polyps or a positive family history of CRC in a first-degree relative after 50 years of age), the recommendation is for a 2–3 years interval. Finally, patients with low-risk (left-sided colitis with endoscopically and histologically excluded signs of active inflammation and patients with CD affecting less than 50% of the colon) are recommended for a 5-year surveillance interval [21]. As a general rule, the surveillance endoscopy should be performed preferentially during remission as the inflammation can mask signs of dysplasia.

As stated above, colonoscopy with random biopsies only is being replaced by high-resolution endoscopy wit targeted biopsies and chromoendoscopy that help to reveal the majority of dysplastic lesions. Chromoendoscopy combines targeted biopsies from abnormal mucosa with random biopsies from each colon segment followed by histology evaluation of the extent of the inflammation. Chromoendoscopy is particularly viable in the detection of flat dysplastic lesions allowing for endoscopic resection of the dysplasia with safe margins which results in lower rates of proctocolectomy. While efficient, the technique is relatively time consuming, costly with a relatively steep learning curve requiring a high number of procedures to acquire expertise. A good bowel preparation is required for successful chromodiagnosis using 0.1% methylene blue or 0.03–0.05% indigo carmine dyes. In contrast, a narrow-band imaging method (often referred to as an electronic chromoendoscopy) has not demonstrated sufficient effect for de-tection of dysplastic lesions in IBD [22].

Dysplastic lesions, including those previously referred to as dysplasia-associated lesions or masses, are evaluated according to the Paris classification defining localization, margins and morphology. Morphological evaluation differentiates polypoid lesions (pedunculated and sessile polyps) and flat lesions (slightly elevated, flat and depressed). Lesions that are assessed as endoscopically resectable should be removed *en bloc* following ink tattoo [23]. The decision to resect should be made based on new techniques of magnification chromoendoscopy, high-frequency ultrasound and confocal endomicroscopy. Only unresectable lesions should be subjected to targeted biopsies. At the same time, biopsies should be taken from areas surrounding the lesion for confirmation of dysplasia. The endoscopically removed dysplastic lesions have a preferable long-term prognosis [24].

Patients with UC and coexisting PSC with the presence of any type of dysplasia or patients with multifocal LGD or HGD in random biopsies are recommended for colectomy. The same is valid in the case of dysplastic lesions that cannot be treated by endoscopic resection (HGD, multifocal LGD, submucosal invasion or recurrent dysplasia). Finally, colectomy should also be recommended for patients that are not in a position to undergo repeated colonoscopy. In all the above cases, the recommendation should always be based on an in-depth discussion with the patient weighing risks against comorbidity and quality of life.

There is no strict instruction for the optimal subsequent colonoscopy surveillance interval for patients after resected dysplastic lesions. It may typically range from 1 month to 1 year with regard to the individual risk factors such as age, duration of the disease, recurrent dysplasia or family history of colorectal cancer [19].

The chemoprevention of IBD-CRC is questionable. A recent meta-analysis of 14 studies has demonstrated a 50% reduction of risk of dysplasia or IBD-CRC in patients taking 5-aminosalicylic acid (5-ASA). Patients with UC taking ursodeoxycholic acid did not significantly lower their risk, however, some reduction was revealed depending on dosage (i.e. dose of < 25 mg/kg/day vs. higher dose). Such observation needs to be further confirmed [4]. There is currently insufficient data on the role of biological therapy (mainly anti-TNF-α and anti-integrins) in the prevention of cancer. It is expected that a lower risk of cancer is a reflection of mucosal healing resulting in shorter exposition to inflammation that would cause malignancy.

Adenocarcinoma associated with UC and ileal pouch-anal anastomosis

Adenocarcinoma associated with UC and in patients undergoing ileal

pouch-anal anastomosis (IPAA) is relatively rare. The risk is dependent on the duration and severity of the inflammation. Past studies have found cumulative incidence of 5, 10, 15, 20 and 25 years from the onset of colitis to be 0.9, 1.3, 1.9, 4.2 and 5.1, resp. A 4-fold increase in the risk of subsequent cancer development was found for patients with dysplasia prior to surgery or a 25-fold increase when adenocarcinoma was found prior to surgery [25].

There are currently no clear guidelines for the management of carcinoma associated with UC and IPAA. A 1-year colonoscopy post-surgical surveillance interval is recommended for high-risk patients with coexisting PSC or those with remaining rectal cuff, LGD or mucosal atrophy of the pouch. A biopsy should always be performed from ileum, ileoanal anastomosis and anorectal mucosa [26].

Small bowel adenocarcinoma

The general frequency of small bowel adenocarcinoma is only approximately 2% of all gastrointestinal cancers. It is, however, 20–30 fold more frequent in patients with CD. The major risk factors in these patients include stenotic and penetrating phenotypes of the disease affecting mainly the jejunum and ileum, the duration of the disease, male gender, therapy by corticosteroids and immunomodulators, but also strictureplasty and small bowel bypass. The risk increases with the presence of dysplasia as a result of adenoma––carcinoma transition. Most of these carcinomas are found by chance during an unrelated CT/magnetic resonance (MR) or are incidental findings during surgical treatment for bowel perforation or obstruction. Surgical resection of the small bowel is therefore an effective modality for lowering the risk of malignant transformation. The effect of preventive use of 5-ASA showing effect in one study is uncertain, as there is no clear evidence for patients on immunosuppressive therapy. Similarly, the prevention by colonoscopy is questionable due to the typical obstructive structures in the small bowel of patients with CD. Despite the absence of clear guidelines for prevention, early detection of neoplasia in the small bowel is possible by special methods of capsule endoscopy, double-balloon endoscopy or CT/MR enterography [1,27].

Anal cancer (spinocellular)

A squamous cell carcinoma of the rectum (anal cancer) is a relatively rare complication of IBD with an incidence ranging from 0.01 to 0.02 per 1,000 patients per year. In IBD patients, anal cancer is typically found in fistulating CD, usually after a long duration of the disease (> 10 years) with late detection. A general increase in risk is reported in homosexual men and in women with severe cervical dysplasia and active HPV infection as well as in immunosuppressed patients after organ transplants. No risk is, however, known for IBD patients with immunosuppression therapy. Due to its poor prognosis, regular colonoscopy evaluations (with special attention aimed at the fistula) with biopsies are recommended. This rare complication should be considered when symptoms are changing or new symptoms arise in patients with perianal CD.

Cholangiocellular carcinoma

The risk of cholangiocellular carcinoma (CoCC) in IBD patients is increased 2- to 4-fold compared to the general population. With coexisting PSC, however, the risk is increased 160-fold. Prevention of CoCC includes imaging of the entire bile tract, preferably by MR cholangiopancreatography or ultrasonography with CA 19-9 marker. Despite the current efforts in methods for early diagnosis, the prognosis of CoCC is very poor. A liver transplant should always be considered when CoCC is suspected in patients with UC with PSC [13,21].

Lymphoproliferative disorders

IBD patients have an increased risk of hematologic malignancies. In UC, the risk of developing leukemias is 2-fold over the general population; patients with CD are mainly at risk of non-Hodgkin's lymphoma. In general, multiple factors contribute to the onset of lymphoproliferative disorders. The duration of IBD is the main factor, especially when diagnosed at a younger age, followed by other factors such as activity and extent of the disease, concomitant presence of an autoimmune disease, Epstein-Barr virus (EBV) infection, male gender and age over 65 years. Lymphoproliferative disorders should always be considered in patients with persisting abnormal values from blood tests, idiopathic febrilias, weight loss, fatigue, adenopathy, hepatosplenomegalia or thromboembolism. A complex diagnostics test should always be performed by a hematologist [21].

Lymphomas represent a special subgroup of IBD-associated disorders in patients treated by immunosuppressives. The risk of lymphomas increases with age and is higher in men. The principal risk factors include concomitant therapy by thiopurines and anti-TNF agents. No increase in lymphoma incidence has been observed for anti-TNF monotherapy [28].

There are three different types of lymphoproliferative disorders associated with thiopurines + anti-TNF therapy of IBD patients:

1. Postransplant-like lymphoma is typical for patients with chronic seropositive EBV, usually over 30 years of age, more frequent in solid organ transplant recipients and thus rare outside transplantation medicine.
2. Post-mononucleosis lymphoma is characteristic for young EBV seronegative males (< 30 years) usually with a fatal course of the disease.
3. Hepatosplenic T-cell lymphoma, a very rare form of peripheral T-cell lymphoma which affects predomi-

nantly younger males (< 30 years) who are treated by concomitant thiopurine/anti-TNF therapy [22]. The CESAME study has revealed a lower risk of this particular type by reduction of such therapy to 2 years. Interestingly, hepatosplenic T-cell lymphoma has not been reported for combined therapy by thiopurines and methotrexate.

To a lesser extent, IBD patients are also at risk of other gastrointestinal cancers. UC has been linked in some cases to hepatobiliary cancers [29], while an increased incidence in gastric cancers was observed for CD [30]. There are extraintestinal cancers that may be linked to IBD [31]. Among them, all types of skin cancers, including malignant melanoma, basal-cell carcinoma and squamous-cell skin carcinoma were identified in association with IBD. Development of malignant melanoma is related to anti-TNF monotherapy with the risk increase of 1.5- to 2-fold compared to the general population. Accordingly, IBD patients should be educated on preventive measures against broad spectrum UV radiation (both UVA and UVB) as well as undergoing frequent skin evaluation by a dermatologist [32]. The risk of NMSC increases with age for smoking white males. While thiopurine therapy also presents a NMSC risk, no such adverse effect was observed for anti-TNF agents. Finally, cervical cancer has been identified as a risk to female IBD patients, especially in connection with smoking, onset of the disease in younger age (< 20 years) and a prolonged use of contraceptives (for over 10 years). The increased incidence of this cervical cancer has mainly been reported in transplant patients on thiopurine therapy [1].

The issue of IBD-associated malignancies has become a multidisciplinary topic that requires the involvement of specialists outside of gastroenterology. The primary aim should be secondary prevention based on surveillance programs. Due to the widespread use of immunosuppressives, the risk of malignant transformation should always be considered. Moreover, thanks to those agents, the average survival rate of the IBD population is increasing, adding a general risk of sporadic cancers. This regularly brings clinicians to a situation where a patient with IBD in need of immunosuppressive or biological therapy also undergoes surgery, chemotherapy or other modality of anticancer treatment. This further emphasises the need for a wide interdisciplinary collaboration among gastroenterologists, pathologists, surgeons, oncologists and, eventually, other specialists. An individual assessment of the therapeutic strategy must always rely on information about the current activity of inflammation, medication, cancer type and stage with respect to and in close collaboration with the patient.

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