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Review Article

Jejunal Adenocarcinoma, A Rare Cancer of The Gastrointestinal Tract: A Comprehensive Review

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Abstract

Jejunal adenocarcinoma is a rare cancer of the gastrointestinal tract. Clinical symptoms are non-specific, making the diagnosis a challenge. Owing to its late diagnosis, curative resection is rare, and the prognosis remains poor. The current 5-year survival rate of small bowel cancer in the United States is 68.3%. Because of the relative rarity of the disease, prospective studies describing clinical characteristics, treatment options, and prognosis are limited. So far, the treatment protocol for jejunal adenocarcinoma has not been standardized. The current review focuses on distilling relevant information that will help clinicians better identify the disease and determine appropriate management strategies.

Keywords: Jejunal Adenocarcinoma; Gastrointestinal Malignancies; Adenocarcinomas; Carcinoids; Lymphomas

Epidemiology

Malignancy of the small bowel is exceedingly rare, accounting for 3%-5% of all gastrointestinal malignancies [1-3]. However, in recent years because of improved diagnostic accuracy, the incidence of small bowel cancer is rising. It is estimated that 10, 470 new cases of primary SI cancer will be diagnosed in the US with 1450 cancer-related deaths [4]. The most frequent histologic types of small bowel malignant tumors include adenocarcinomas, carcinoids, lymphomas, and sarcomas. Adenocarcinoma of the small intestine is the second most common histologic type of SI cancer. The most frequent location of SI adenocarcinoma is the duodenum (57%), followed by jejunum (29%) and ileum (13%) [5]. SI cancers are more common in men than women [6]. They occur more commonly in the African American population and after 60 years of age [7].

There are several hypotheses to explain the relatively low incidence of SI cancers. Unlike the large intestine, a rapid transit time in the small intestine decreases' exposure to luminal toxins and carcinogens. The presence of the enzyme benzopyrene hydroxylase in the intestinal mucosa aids in the detoxification and production of fewer reactive oxygen radicals in the small intestine. Further, bacterial enzymes also have oncogenic potential. A relatively low prevalence of bacteria in the small intestine is postulated to protect against carcinogenesis. The small intestine has one of the largest reserves of lymphoid tissue that confers immune surveillance against neoplastic cells. Finally, the rapid turnover of cells in the intestine is instrumental in clearing apoptotic bodies that have tumorigenic potential [8].

Risk Factors

Lifestyle factors

Alcohol consumption, cigarette smoking, and dietary factors including a low fiber diet and increased intake of processed meat

and high-fructose-containing drinks are associated with increased odds of small bowel adenocarcinoma [9]. Alcohol use is associated with other gastrointestinal cancers of the esophagus, colon, and rectum [10]. It can interfere with DNA methylation, which influences cancer growth [11]. Since ethanol can also act as an irritant to the intestinal mucosa, it can increase susceptibility to carcinogens [12]. It has also been shown that acetaldehyde, the primary metabolite of ethanol, is genotoxic. In addition to alcohol, carcinogenesis with tobacco use occurs via several mechanisms. It can lead to the deposition of nitrosamines in the small intestine, a reduced cellular immune response, and impaired induction of enzymes that detoxify polycyclic aromatic hydrocarbons [13]. The resultant accumulation of reactive oxygen species predisposes to cancer.

Familial Syndromes

Several hereditary cancer syndromes can predispose to developing SI adenocarcinomas. Familial adenomatous polyposis (FAP) is a pre-cancerous condition associated with an increased risk of duodenal and periampullary neoplasms and early colorectal carcinoma requiring periodic surveillance. It is an autosomal dominant condition characterized by a germline mutation in the APC gene, located on chromosome 5q21 [14]. APC is a member of the Wnt/B-catenin signaling pathway that is frequently implicated in colorectal cancer. When compared with the general population, patients with FAP are associated with an elevated relative risk (RR) of duodenal adenocarcinoma (RR, 331; 95% CI 132-681) [15]. Ruys et al described 3 cases of jejunal adenocarcinoma that developed in patients with FAP and advanced duodenal adenomatosis [16]. The same group later performed a prospective enteroscopic evaluation in 13 patients with FAP and advanced duodenal polyposis (Spielman stage IV). Only one patient was reported to have large polyps covering one-third of the jejunal circumference and the group concluded that clinically significant jejunal polyposis was rare and routine jejunal evaluation in FAP patients was not warranted [17].

Lynch syndrome or Hereditary nonpolyposis colorectal cancer (HNPCC), an autosomal dominant disease, occurs due to germline mutations in DNA mismatch repair (MMR) genes that can predispose to not only cancers of the small intestine but also colorectal, endometrial, gastric, ovarian, biliary, and skin [18]. It is associated with a 4% lifetime risk of developing small bowel neoplasia, which predominantly involves the distal small bowel [19]. Deficiency of MMR gene results in microsatellite instability (MSI). The National Comprehensive Cancer Network (NCCN) endorses universal MMR or MSI testing of all patients with a personal history of SI adenocarcinoma to identify individuals with Lynch syndrome. Puetz-Jeghers syndrome (PJS) is an autosomal dominant condition caused by an inherited mutation of STK11. It is characterized by multiple hamartomatous and adenomatous gastrointestinal polyps, predominantly located in the jejunum and ileum [20,21]. At-risk individuals have a relative risk of 520 for developing SI adenocarcinoma when compared with unaffected individuals [22]. The lifetime risk of SI adenocarcinoma has been estimated between 1.7% and 13% for individuals with PJS [23, 24].

Crohn's disease and Celiac disease

Proinflammatory conditions like Crohn's disease and celiac disease can also predispose to SI adenocarcinoma through an adenoma-carcinoma sequence [25, 26]. The risk of adenocarcinoma of the small intestine was modestly increased (10-fold) in a large population-based study of patients with celiac disease in Sweden [27]; however, the association with celiac disease remains poorly understood. Crohn's disease is associated with adenocarcinoma of the distal small bowel, particularly the ileum. Von Roon et al described the relative risk of small intestinal cancer as 28.4 in patients with Crohn's disease, with a mean duration of nine years prior to the development of carcinoma [28]. There are case reports of an association between proinflammatory conditions and jejunal adenocarcinoma but no large-scale RCTs have been performed [29,30].

Pathology and Staging

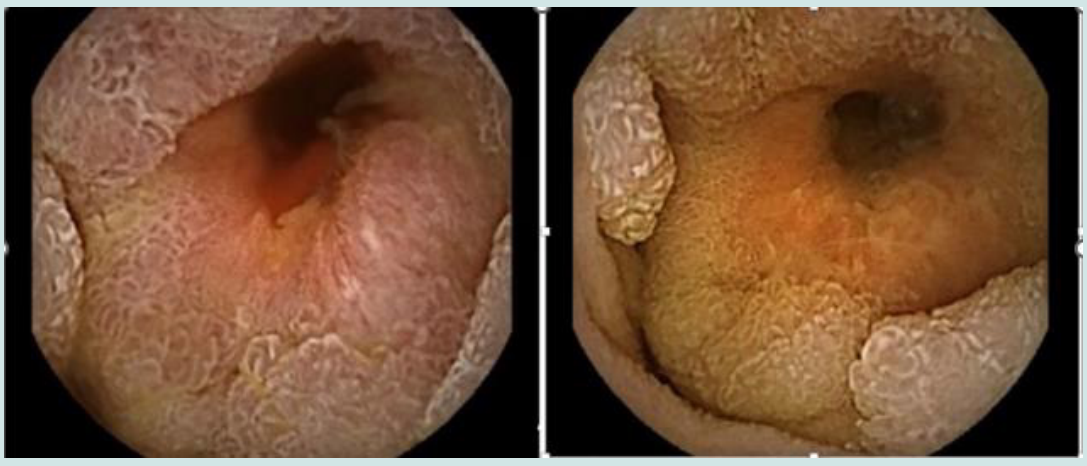

Figure 1: Video capsule endoscopy demonstrating a circumferential mass lesion in the proximal jejunum.

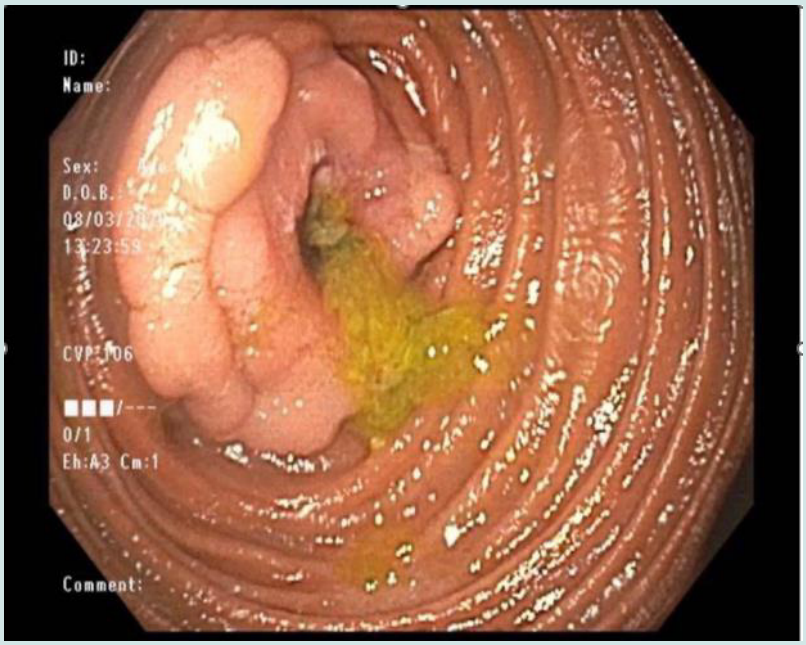

Figure 2: Push enteroscopy showing a circumferential friable mass in the proximal jejunum.

SI adenocarcinomas grossly appear as stenosing, ulcerative, infiltrative, or polypoid lesions (Figure 1&2). The histopathologic evaluation shows well to poorly differentiated tumors with a variable degree of mucin secretion. The American Joint Committee on Cancer (AJCC) stages SI adenocarcinoma in accordance with tumor size (T), regional lymphadenopathy (N), and the presence or absence of metastasis (M). Based on the extent of the disease, they are classified into 5 stages with tumor staging having a significant impact on survival: 72 months for stage I and stage II, 30 months for stage III, and 9 months for stage IV adenocarcinoma. The AJCC reported 5-year survival rates of 55% for stage 1, 49% for stage IIA, 35% for stage IIB, 31% for stage IIIA, 18% for stage IIIB, and 5% for stage IV tumors [31].

Clinical Presentation and Diagnosis

Bridge et al described the clinical and pathological features of 32 adenocarcinomas of the jejunum [32]. Patients with jejunal adenocarcinoma may be asymptomatic or have non-specific symptoms such as intermittent abdominal cramping or pain, nausea, vomiting, or weight loss. Based on the size, location, and blood supply, adenocarcinomas of the jejunum can present with intestinal obstruction or occult gastrointestinal bleeding. At the time of diagnosis, more patients with jejunal adenocarcinoma are reported to be symptomatic when compared to duodenal adenocarcinoma (84% vs 57%) [33]. Because of non-specific symptoms, there is a significant delay in diagnosing disease averaging 7 to 8 months from onset of symptoms [34]. Several diagnostic modalities are available to evaluate small intestinal lesions. Barium studies are not particularly effective in identifying distal small intestinal lesions with a sensitivity of 50% [35].

In contrast, computed tomography (CT) enterography and Magnetic resonance (MR) enterography have the advantage of providing multiplanar cross-sectional imaging over enteroclysis with a sensitivity of 100%. A prospective study comparing CT enterography to MR enterography in 150 patients with suspected small bowel disease reported that MR enterography was more accurate than CT enterography, particularly for neoplastic diseases (P=.0412) [36]. Video capsule endoscopy (VCE) and enteroscopy are the preferred diagnostic modalities to provide direct visualization of jejunal lesions. Zhang et al reported a higher detection rate of SI tumors with DBE when compared to VCE [37]. VCE allows complete visualization of the small bowel mucosa and is particularly effective in diagnosing lesions in patients with obscure GI bleeding with a detection rate of 4% to 9% [38]. In the case of small bowel obstruction or stricture, enteroscopy is the preferred diagnostic technique owing to the risk of capsule retention.

Molecular Mechanisms

Genetic alterations in SI adenocarcinomas are not very well documented. K-ras mutations were more common in jejunal adenocarcinoma (43% to 47%), while p-53 mutations are more common in duodenal adenocarcinoma (41% to 48%) [39]. While ras genes regulate intracellular signaling pathways by encoding guanine nucleotide-binding proteins, K-ras activation has demonstrated oncogenic potential. Inactivation of p-53 tumor suppression genes and resultant deletion of chromosome 17p results in dysregulation of apoptosis. A mutation in the APC gene, a component of the Wnt/ B-catenin signaling pathway, that is frequently linked with colorectal cancer is seen increasingly associated with periampullary tumors and duodenal tumors. Microsatellite instability arising from a deficiency in MMR gene in

Lynch syndrome can be found in 5% to 35% of SI adenocarcinomas, predominantly affecting the distal small bowel [40].

Treatment

There are no prospective randomized trials that have evaluated surgery for the treatment of primary SI adenocarcinoma, but retrospective reviews have been reported. The type of surgical resection used to treat localized cancer depends on the location of the tumor. Surgical resection with en-bloc removal of regional lymph nodes offers the best chance of overall survival in patients with local (stage I-III) jejunal adenocarcinoma. The rate of curative resection (R0) is 64% to 97% with a median survival time of 19 months [41,42]. The 5-year cancer-specific survival rates were 66% for jejunal lesions [43]. After surgical resection, local and distant recurrences are common. The role and efficacy of chemotherapy in various stages of SI adenocarcinoma remains unclear.

The phase III BALLAD trial is the first prospective study evaluating the role of adjuvant 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) compared with observation alone for patients with stage I-III disease [44]. The results of the BALLAD trial are yet to be reported, meanwhile, data from retrospective studies are limited. There are no phase 3 clinical trials assessing the efficacy of chemotherapy in unresectable and stage IV jejunal adenocarcinoma. Retrospective studies with 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen report an overall survival of 20 months for stage III disease and 12 months for stage IV jejunal adenocarcinoma [45]. Currently, the NCCN recommends systemic therapy for advanced SI adenocarcinoma. There are three chemotherapy regimens: FOLFOX, capecitabine plus oxaliplatin (CAPEOX), or 5-fluorouracil, leucovorin, oxaliplatin, irinotecan (FOLFOXIRI), any of which may be combined with bevacizumab for patients with advanced disease who are appropriate for intensive therapy. For patients who are not appropriate for intensive therapy, treatment options would include 5-fluorouracil and leucovorin or capecitabine with or without bevacizumab [46].

Prognosis

Overall survival in SI adenocarcinoma is significantly correlated with tumor location, staging, age of the patient, surgical resection, and history of Crohn's disease [47]. The most important independent prognostic factors on a multivariate analysis include curative resection (R0), lymph node involvement, and the ratio of positive to negative lymph nodes [48]. In patients undergoing curative resection, a poor prognosis was associated with patients who are older than 55 years of age, African American heritage, duodenal or distal or diffuse tumor localization, advanced TNM stage, metastatic, poorly differentiated, or involved margins [49]. Several studies suggest that jejunal tumors have a better prognosis than a duodenal tumor.

Conclusion

In conclusion, adenocarcinoma of jejunum is a rare cause of iron deficiency anemia. Considering its non-specific presenting symptoms, a high index of suspicion should be maintained, particularly when an EGD and colonoscopy do not exhibit the source of bleeding. Risk factors include environmental, familial and chronic inflammatory conditions. Curative surgical resection is the treatment of choice for localized cancer, while systemic chemotherapy is reserved for advanced disease.

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