DOI 10.21680/2179-7889.2024v15n2ID38622

ADENOCARCINOMA OF SMALL BOWEL: WHY IS IT SO RARE

Adenocarcinoma do intestino delgado: Porque é tão raro

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Work performed at the Department of Surgery, Federal University of Rio Grande do Norte (UFRN), Brazil.
Financial support: None.
Conflicts of interest: None.
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Submitted: dec 21; accepted after revision, dec 22, 2024.

ABSTRACT

Small bowel adenocarcinoma (SBA) is a rare gastrointestinal neoplasm and despite the small intestine's significant surface area, SBA accounts for less than 3% of such tumors. Early detection is challenging and the reason arises from its asymptomatic nature, often leading to late-stage discovery and poor prognosis. Treatment involves chemotherapy with a 5-fluorouracil combination, but the lack of effective chemotherapy contributes to a generally poor prognosis. SBAs are linked to genetic disorders and risk factors, including chronic inflammatory conditions. The unique characteristics of the small bowel, such as rapid cell renewal and an active immune system, contributes to the rarity of these tumors as well as the high intratumoral infiltration of immune cells is associated with a favorable prognosis. Microsatellite instability in SBA is associated with a high tumor mutational burden, affecting the prognosis and response to immunotherapy. The presence of PD-L1 and programmed cell death, along with tumor-infiltrating lymphocytes, plays a crucial role in the complex microenvironment of SBA and contributes to a more favorable prognosis, especially in the context of high MSI tumors. Stromal tumor infiltrating lymphocytes are identified as independent prognostic indicators and the association between MSI status and a favorable prognosis, emphasizes the importance of evaluating the immune status of tumors for treatment decisions. In conclusion, small bowel adenocacinoma is a rare disease, the organ has some caracteristics that contributes to the small incidence of SBA. Finally, the diagnosis, treatmentand survival are challenging.

Keywords: small bowel, adenocarcinoma, tumor incidence, treatment, prognosis, immunology

RESUMO

O adenocarcinoma do intestino delgado é uma neoplasia gastrointestinal rara e, apesar da área de superfície significativa do intestino delgado, o tumor é responsável por menos de 3% dos tumores do tracto digestivo. A detecção precoce é desafiadora por sua natureza assintomática, muitas vezes levando à descoberta em estágio tardio e prognóstico ruim. O tratamento envolve quimioterapia com uma combinação de 5-fluorouracil e outras drogas, mas a falta de quimioterapia eficaz contribui para um prognóstico geralmente ruim. Os adenocarcinomas do intestino delgado estão ligados a distúrbios genéticos e fatores de risco, incluindo condições inflamatórias crônicas. As características únicas do intestino delgado, como rápida renovação celular e um sistema imunológico ativo, contribuem para a raridade desses tumores, bem como a alta infiltração intratumoral de células imunes associada a um prognóstico favorável em certos casos. A instabilidade de microssatélites no SBA está associada a uma alta carga mutacional tumoral, afetando o prognóstico e a resposta à imunoterapia. A presença de PD-L1 e morte celular programada, juntamente com linfócitos infiltrantes de tumores, desempenha um papel crucial no microambiente complexo do SBA e contribui para um prognóstico mais favorável, especialmente no contexto de alguns tumores. Linfócitos infiltrantes de tumores estromais são identificados como indicadores prognósticos independentes e um prognóstico favorável enfatiza a importância de avaliar o estado imunológico dos tumores para decisões de tratamento. Em conclusão, o adenocacinoma do intestino delgado é uma doença rara, e o órgão tem algumas características que contribuem para a sua pequena incidência. O diagnóstico, tratamento e sobrevivência são desafiadores.

Palavras-chaves: Intestino Delgado, Adenocarcinoma, Incidência de Tumores, Tratamento, Prognóstico, Imunologia.

INTRODUCTION

Small bowel malignant disease represent a group of histologically diverse tumours. Carcinoids, adenocarcinomas, lymphomas and sarcomas represent the common histological small bowel types, which have a varied distribution across the three anatomical segments of the small intestine: duodenum, jejunum and ileum[1]. This Review focus exclusively on small bowel adenocarcinomas. We summarize the existing knowledge of this malignancy and highlight the recent advances in the molecular understanding of the disease, together with diagnostic approaches and therapeutic options. Small bowel cancers have received relatively little attention, both in terms of clinical cognizance and research efforts. The incidence of small bowel cancers is rising and their epidemiological landscape is changing[2]. Carcinoids, that comprise 44% of all small bowel cancers, currently constitute the dominant histology whereas

adenocarcinomas represent approximately one-third of all small bowel cancers[3].This literature review aimed to evaluate why small bowel adenocarcinoma is so rare, compared to the stomach and colon.

METHODS

The research methodology for this text was designed to investigate why the small bowel adenocarcinoma is so rare. Multiple reputable databases were utilized to ensure coverage of relevant scientific and medical literature, including PubMed, Scopus, SciELO, Embase, and Web of Science, which were recognized for their extensive collections of peer-reviewed publications. Google Scholar was employed to access significant studies not available in standard academic journals. Search parameters were carefully crafted using relevant keywords such as “small bowel," "adenocarcinoma”, "tumor incidence," "treatment," "prognosis," and "immunology." This strategic combination of search terms ensured the retrieval of studies directly pertinent to the research objectives. Inclusion criteria encompassed a broad spectrum of study designs, including cohort studies, case-control studies, systematic reviews, and meta-analyses. This approach aimed to capture diverse evidence and perspectives on bowell adenocarcinomas. Exclusion criteria were established to filter out studies focusing on unrelated diseases. This literature review provided a solid foundation for evaluating and synthesizing the findings. It ensured that this study's conclusions were based on a comprehensive and critically assessed evidence regarding small bowel adenocarcinoma.

Epidemiology

Malignant tumors of the small intestine are very rare throughout the world. Global incidence is less than 1.0 per 100,000, ranging from 0.3 to 2.0 per 100,000, when considered the world population[4]. The small bowell (SB), consists of the duodenum, jejunum and ileum, represents 75% of the length, about 6–8 meters, extending from the pylorus to the ileocecal valve. It represents 90% of the absorptive surface area of the esophago-gastrointestinal system. Only 2% of the total annual cancer incidence of the digestive system occurs in the SB. In contrast, approximately 57% of cancers in the digestive system are diagnosed each year in the colon, which measures about 1.5 meters in length[5]. Small bowel adenocarcinoma (SBA) accounts for a 30–40% incidence of small bowell cancers (SBC). As diagnosis is not so easy, It has a poor prognosis compared to other SBC histologic subtypes, with overall survival of around 10% for stage IV and about 63–32% for stages I–III[6-8]. About 50% of SBCs arise in the duodenum, followed by the jejunum (30%) and ileum (15%)[3]. Some risc factors have to be described: SBA is associated with advanced age, inflammatory bowel disease, and coeliac disease. Its rarity comes in contrast with the facts that small intestine constitutes 95% of the surface area of the entire gastrointestinal tract. It represent less than one-third of all small bowel cancers. Although SBA found throughout the length of the small intestine, more than half (56%) are located in the duodenum[3]. Paradoxically, the disease is common in the stomach and colon. When considering all neoplasms that affect the small intestine,

it is observed that adenocarcinomas, constituting around 40% of malignant small bowel tumors[9-11]. SBA presents a challenge in terms of early detection, as it is frequently asymptomatic for several months, leading to late-stage discovery and poor prognosis. Its detection often arises from complications such as intestinal perforation, ileus, and unbridled gastrointestinal hemorrhaging. By the time of the diagnosis, nearly one-third of individuals have distant metastasis and an advances stage. Imaging techniques are not conclusive, and upper digestive endoscopy does not reach the small intestine. All that remains is the use of capsule endoscopy. It has high cost and it is not available in many countries, or hospitals Around the world[12-14]

One example of a patient with intestinal semi-obstruction of jejunum may be observed in the figure 1-A-B. The adenocarcinoma was diagnosed by using contrast examination of the small intestine (bowel transit), which can be available in Figure 1A. The patient underwent enterectomy. There were signs of jejunal subocclusion, which resulted in dilation of proximal jejunal loops. After enterectomy, the open surgical specimen clearly demonstrated the appearance of adenocarcinoma (Figure 1-B), confirmed by histopathological examination. This is the only case of jejunal adenocarcinoma in the space of 5 years in a large hospital, demonstrating the rarity of the disease.

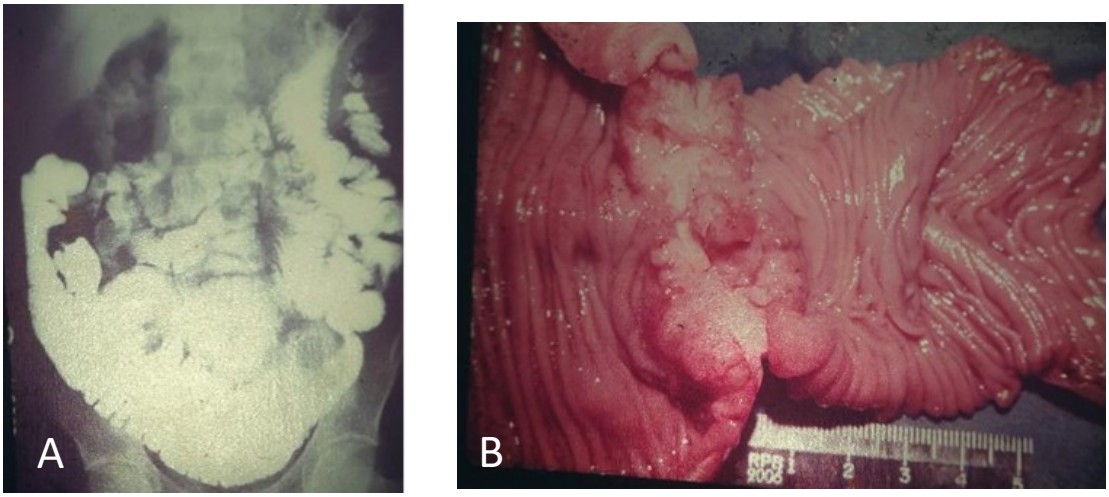

Figura 1
A - Bowel transit examination showing semi-occlusion of the jejunum.
B - Open surgical specimen, showing jejunal tumor. Dilated jejunal loop on the left side of the figure

ANATOMICAL AND PHYSIOLOGICAL FACTORS

The small bowel has a unique characteristics, including rapid epithelial cell renewal, preventing the accumulation of genetic damage of mucosa.

The unique microenvironment of the small intestine protects it against carcinogenic stimuli. It has a low bacterial load, dilute liquid contents and relatively rapid transit time, that decreases the amount and duration of exposure to carcinogens in the

small intestine. Additionally, higher levels of lymphoid aggregates and IgA levels in the small intestine compared to the colon, might confer better tumour immunity and surveillance[15,16].

The aetiology of most SBA remains nuclear. Both familial cancer syndromes and conditions associated with increased small bowel inflammation, such as coeliac and Crohn's disease, are responsible for a small number of patients who develop small bowel adenocarcinomas[17-19].

HISTOLOGY

The mucosal layer of the small intestine is replaced in 4–7 days (12) and consists of absorptive, glandular, and neuroendocrine cells that line the crypts and villi. The crypt epithelium functions in cell proliferation and cell renewal. Pluripotential stem cells are located at the base of each crypt, from which undifferentiated reserve cells migrate toward the lumen and differentiate into absorptive cells or enterocytes, or into mucin-secreting. The villi are mucosal folds of columnar epithelial cells that amplify the absorptive surface area of the intestinal lumen. The tunica mucosa of the villi rests on a basement membrane, lamina propria, and muscularis mucosa. The lamina propria contains lymphocytes, macrophages, and plasma cells. They are responsable for tne secretion of immunoglobulin IgA that diffuses into the intestinal lumen and lamina propria. Mucosa-associated lymphoid cells are scattered throughout the mucosa of the small intestine, and in the ileum is rich in macroscopic Peyer patches. Antigens that gain access to mucosal macrophages and Peyer patches activate B and T lymphocytes that function as antigen responsable to immunosurveillance. They acts protecting intestine against infection and cancer[20].

IMMUNOLOGICAL FACTORS - PATHOGENESIS

The pathogenesis of SBA is not well understood; however, mutations in p53, β-CATENIN, APC, BRAF, and MMR genes have been implicated in SBA development[21]. Moreover, the KRAS mutation rate in SBA is comparable to that observed in CRC (40–60%), while BRAF mutations are infrequent in SBA[17,22].

An active immune surveillance as it is the largest organ of the immune system, contribute to the rarity of these tumors. High intratumoral infiltration of CD3+ and CD8+ cytotoxic T-lymphocytes, along with the presence of tertiary lymphoid structures, is associated with a favorable protection of small bowell agaist adenocarcinoma[23].

Some studies have shown the efficacy of blocking the PD-1/PDL1 signaling pathway in gastrointestinal cancers with high MSI (MSI-H), establishing a significant association between MSI-H and PD-L1 expression in small bowell adenocarcinoma. Some studies suggest a favorable prognosis associated with PD-L1 expression. The abundance of tumor-infiltrating liphocytes (TILs) has been linked to improved survival, emphasizing the crucial role of the immune system in combating small bowel cancers[9].

The presence of PD-L1 and PD-1 in small bowell adenocarcinomas (SBA), in contrast to other cancer types, contributes to a more favorable prognosis. Patients with SBA and MSI-H tumors exhibit superior overall survival. Similarly, individuals with elevated stromal tumor-infiltrating lymphocyte (sTIL) levels in SBA demonstrate extended overall survival times.

In SBA, the presence and activity of TILs are of particular interest, as they are implicated in both the progression and potential control of the disease. Increased percentages of TILs are also correlated with the infiltration of B cells, dendritic cells, and natural killer cells, enhancing the immune response in small bowell adenocarcinomas[22]. According to the multicenter cohort of Noh *et al*, a best prognosis was observed in patients with high PD-L1 and high CD8+ TILs in SBA[23].

ADENOCARCINOMAS

Adenocarcinomas may appear as polypoid, infiltrating, or as annular constricting lesions. Similarly to tumors in the colon, the adenoma in the small intestine is a precursor of adenocarcinoma . Residual adenomatous tissue is observed commonly at the margins of sporadic carcinomas, and of carcinomas in patients with familial adenomatous polyposis[24]. The pathogenesis of invasive adenocarcinoma in the small intestine involves mutational and epigenetic pathways that simulate the multistep events in colorectal neoplasia. Mutations have been reported in adenomatous polyposis coli, β-catenin, E-cadherin, K-ras, p53, and 18q alleles that presumably participate in the adenoma-carcinoma histogenesis pathway[25].

Mutations at the adenomatous polyposis coli 5q locus occur infrequently in small intestinal neoplasia, in contrast to their higher prevalence in colorectal adenomas and carcinomas. The great number and diversity of microorganisms in the intestinal tract are important in the development of gut-associated lymphoid tissue and immune capacity[26].The intestinal bacteria provide the metabolic capacity to facilitate xenobiotic transformation and potential synthesis of carcinogenic metabolites. Intestinal anaerobic microorganisms produces various metabolizing enzymes, such as β-glucuronidase, βglucosidase, sulfatase, nitrate and nitro reductases, and decarboxylases, which act on various substrates such as the bile acids, fatty acids, and steroid molecules. The conversion of ingested chemical agents to genotoxic molecules has been investigated in antibiotic-treated rodents. In fact, cycasin, a methylazoxymethanol glucoside, is not tumorigenic when administered parenterally or orally to germ-free rats. However, when fed orally to rats with normal intestinal microbial flora, less than 50% of the conjugated compound was recovered in the feces and urine, and adenocarcinomas were induced in the colon, and other organs such as liver, biliary duct system, and kidney. Microbial β-glucosidase had converted cycasin to unconjugated methylazoxymethanol, an active mutagenic and tumorigenic metabolite[27,28].

TREATMENT – SURVIVAL

SBA is a challenging disease to treat, and its management is based on the site and stage of disease at presentation, patient comorbidities, performance status, and available expertise. Surgical resection is the principal strategy of management for resectable disease. Nevertheless, approximately 64% of SBC patients could undergo a complete resection. SBA has (62%) potential for curative resection. Complete resection offers the longest survival and is considered a significant prognostic predictor of overall survival. The recurrence of SBA is common, and the outcome after recurrence is a great problem[28].

In conclusion, small bowel adenocacinoma is a rare disease, the organ has some caracteristics that contributes to the small incidence of SBA. Finally, the diagnosis, treatmentand survival are challenging.

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