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Case Report

Occult small bowel adenocarcinoma in Crohn's disease-more than a simple stricture

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ABSTRACT

Small-bowel adenocarcinoma (SBA) accounts for less than 5% of all gastrointestinal cancers. It is generally linked to genetic disorders and immune-mediated inflammatory conditions like Crohn's disease (CD). Despite advances in oncology, SBA has a poor prognosis and high relative risk in this subgroup of patients. Risk factors for the development of SBA in patients with CD include a stricture phenotype and a long- standing disease. This article aims to expose a case of association between CD and SBA and its management. A 66-year-old woman with long-standing terminally ileum-affected CD with multiple admissions due to sub-occlusive episodes and weight loss. CT and MRI revealed intestinal thickening in the small bowel, suggesting an inflammatory stenosis and entero-enteric fistulous tracts. An ileocolectomy was performed, and the patient's histopathological evaluation revealed a mucinous invasive adenocarcinoma of the terminal ileum. The patient was treated with adjuvant chemotherapy and has been under surveillance for two years, without malignant recurrence. Although it is a relatively rare neoplasm, CD patients have a significant risk of developing SBA, when compared to the general population. Diagnosis is challenging due to the occult nature of CD-associated SBA, and imaging and endoscopy alone make it difficult to detect the pathology. Treatment involves a high index of suspicion for the diagnosis and a balance between extended mesenteric resection and CD surgery's primary idea of bowel length preservation. Despite recent advances in oncology, the survival rate in CD-SBA patients remains low. Long-standing CD patients should have the terminal ileum monitored regularly and surgeons should be aware for occult SBA. Post-resection patient surveillance involves regular abdominal exams, serial surveillance, cross-sectional imaging, and monitoring for obstructive symptom recurrence. There is a lack of clear guidelines for primary prevention and surveillance of SBA, with a focus on inflammation management. Preoperative diagnosis techniques are scarce, and patients risk suboptimal treatment if incidental cancer is found. Strategies include right mesenteric-based surgical techniques and/or frozen section exam, always balancing cancer treatment and bowel preservation which is of high relevance in this subgroup of patients.

Keywords: Inflammatory bowel diseases, Crohn disease, ileal adenocarcinoma, small bowel adenocarcinoma

INTRODUCTION

Small-bowel adenocarcinoma (SBA) is a relatively uncommon malignancy, yet it represents the most prevalent form of cancer affecting the small bowel. Although sporadic SBA accounts for <5% of all gastrointestinal cancers, it's the most common form of this malignancy in the small bowel. Only a small proportion of them are linked to genetic disorders such as familial adenomatous polyposis (FAP), MUTYH Polyposis, Juvenile Polyposis, and Lynch or Peutz-Jeghers syndromes.[1] Additionally, SBA may develop in individuals with immune-mediated inflammatory conditions, including coeliac disease or inflammatory bowel disease (IBD), specifically CD.[2] IBD-associated SBA was first described by Ginzburg et al in 1956, and its frequency is estimated at ~1.6% of all small bowel malignancies.[3]

Indeed, individuals diagnosed with IBD are at increased susceptibility to develop gastrointestinal and, to a lesser extent, extraintestinal malignancies. This risk appears to be influenced by the management of the underlying inflammation and is possibly associated with the administration of immunosuppressive (IMS) therapy.[4] Despite improvements in oncology, CD-SBA has a poor prognosis. Indeed, among these malignancies, SBA has the highest relative risk and the lowest 5-year overall survival rate, despite its low absolute risk.[2]

The aim of this work is to present the clinical case of a mucinous ileal adenocarcinoma implanted in CD.

Genetics

For decades, IBD-related SBA was thought to be caused by a chronic inflammation-dysplasia-carcinoma sequence, different from colorectal carcinomas. However, advanced molecular studies have shown that specific genetic changes are critical in disease pathogenesis and can predict prognosis.[5]

A recent large study examined 76 SBA patients with either CD, coeliac disease, or sporadic occurrences. Through multivariate analysis, they revealed several predictive variables, including KRAS mutations, microsatellite instability, tumor-infiltrating lymphocytes, and HER2 gene variations.[6] Besides, when considering all patients, celiac disease patients had a better prognosis.[6] This molecular classification technique can improve therapeutic targeting and should be widely used.

Risk factors

Despite the previously explained genetic linkages, there are several well-known risk factors associated with the development of this malignancy in CD patients. The most significant ones seem to be the stricture CD phenotype and the long-standing disease.[2] Other less predominant risk factors include male gender, youthful age at diagnosis, smoking, distal jejunal/ileal localization, small-bowel bypass loops, and the use of steroids and immunomodulators.[4,7,8] On the other side, there is some evidence that also reveals that the use of amino-salicylates for a duration beyond two years may be associated with a statistically significant decrease in the occurrence of SB.[9]

This article aims to expose a case of an association between an IBD and an oncological disease, which, although rare, is known to be associated and to have a poor prognosis.

CASE REPORT

Herein, the case of a 66-year-old woman with a medical history of CD, chronic obstructive pulmonary disease (COPD), treated with bronchodilators, and bronchiectasis is presented.

From a surgical background, she was previously subjected to left hemithyroidectomy, lower left parathyroidectomy, laparoscopic cholecystectomy, and lung lobectomy with upper right lobe atypical atelectasis resection. She is a patient with CD diagnosed in 2010 (11 years of evolution) with a predominantly terminally ileum-affected disease with a penetrating and stenosing pattern: A3L3B2/3 (Montreal classification). Despite the control of the disease with IMS therapy (Vedolizumab), in the last year the patient had several sub-occlusive episodes, requiring hospitalization, and a weight loss of about 10 kg. These sub-occlusive episodes were conservatively treated, including two weeks of enteral nutrition by naso-jejunal probe. In this context, she performed CT and magnetic resonance imaging (MRI) that revealed areas of parietal intestinal thickening in the small bowel, namely in the region of the last ileal segment in about 6 cm of longitudinal extension, intercalated with a 5 cm segment without alterations, and near this, a new area of parietal thickness, which forms a conglomerate with other enteric bowel segments but without parietal distension between them and with retraction, suggesting the presence of entero-enteric fistulous tracts. These changes cause ectasia of the upstream loops, which reach approximately 45mm in larger caliber (Figure 1).

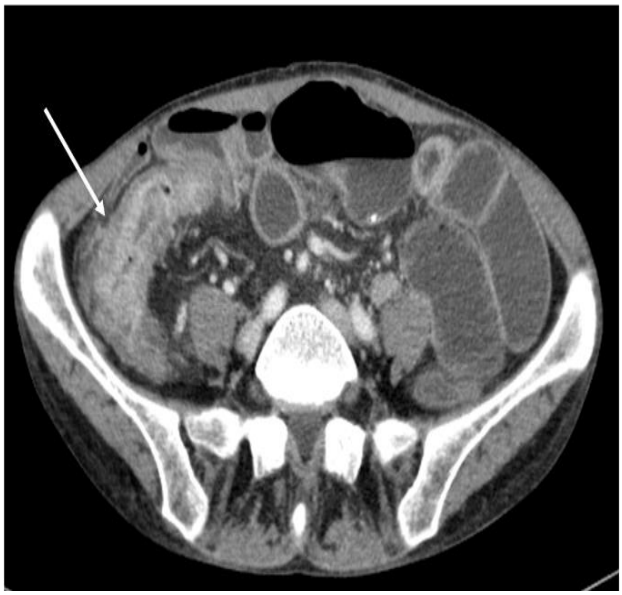

Figure 1: The abdominopelvic CT-scan performed by the patient, in the context of intestinal sub-occlusive episodes. The arrow shows areas of parietal ileal thickening, as previously mentioned.

The case was discussed with a multidisciplinary team, and the patient was proposed for surgery.

Intraoperatively, a large mass in the terminal ileum, involving the ileocecal valve, adherent to the ileo-cecal appendix, middle transverse, and another adjacent ileal segment, with consequent dilation of the entire small bowel was identified.

Furthermore, there were multiple enlarged lymph nodes in mesentery, next to ileocolic vessels. Macroscopic secondary liver lesions were not identified, but there were whitened milia areas in visceral peritoneum around mass, interpreted in context of inflammatory alterations. Note that there was no preop diagnosis of malignant disease.

An ileocolectomy was performed, with mechanical laterolateral ileocolic anastomosis. The patient evolved favorably without complications in the post-operative period. The specimen histopathological evaluation was compatible with a mucinous invasive and moderated differentiated adenocarcinoma of the terminal ileum, with a maximum tumor thickness of 12 mm and maximum tumor diameter of 6.5 cm of longitudinal extension. The margins were cleared with a longitudinal margin of 4 cm relative to the distal top, more than 4 cm relative to the proximal top and a radial margin of 6.5 cm. The tumor invaded the subserous and mesenteric fat, with vascular and perineural invasion, but no tumor perforation was seen. Of the 35 excised lymph nodes, eight were positive for carcinoma, and there were one subserous 8 mm fat tumoral deposit. The expression of the four-mismatch repair (MMR) proteins (MLH1; PMS2; MSH2 and MSH6) was maintained, with low probability of microsatellite instability (MSI-H). Also, it was possible to identify chronic transmural inflammatory lesions of the ileal wall, with focal ulceration of the mucosa, in a non-neoplastic area, and fistulous tracts between adjacent small bowel segments, compatible with CD. The case was discussed within the institutional multidisciplinary team, and since its stage (stage III - pT3G2N2M0), it was decided to complement treatment with adjuvant chemotherapy with the CAPOX protocol (Capecitabine and oxaliplatin), which the patient completed during 6 months with good tolerability.

The patient has been under surveillance for two years, with blood tests and CT-scan and endoscopy, with no evidence of tumor recurrence or new occlusive episodes. She also performed positron emission tomography (PET-scan) that revealed diffuse colon capture compatible with Crohn reactivation, but without lesions suggesting metastasis. The carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9) levels were normal during all the case evolution.

DISCUSSION

The risk

As previously discussed, there is an important risk of developing this malignancy in CD patients. A recent meta-analysis of population-based cohort studies revealed a CD-associated SBA risk of 0.08%, corresponding to a 27-fold increase relative to the general population.[3] In another large meta-analysis comprising 20 studies, the relative risk for SBA in individuals with CD was 18.7-fold when compared to a background equivalent population (1 per 3000 patients/year).[7] A large French nationwide cohort study also revealed that the risk for SBA appeared to be greater in patients who have been diagnosed with CD for over 8 years, increasing its standardized incidence ratio to 46-fold.[10]

SBA in CD vs. sporadic cases

Besides its known connection, it's also important to note that there is a wide range of severity for SBA in CD when compared with sporadic cases. Fields et al. present the overall survival rate of a sizable cohort of SBA patients, 4093 of whom have CD, obtained from the US national cancer data base between 2004 and 2016. When compared with sporadic cases, patients with SBA and CD were substantially younger, had more frequent ileal involvement, and had more poorly differentiated tumors.[11] When compared with the present case, this patient had 11 years of disease evolution, with predominantly ileal involvement, but the tumor was moderately differentiated. Although overall survival was comparable, the stage of disease, co- morbidities, positive surgical margins, a higher tumor grade, older age, and a lack of chemotherapy treatment substantially impacted survival. Survival at five years was a dismal 36.5% on average and was unmistakably correlated with disease stage, with patients in stages III and IV of CD exhibiting a declining trend in survival. Regrettably, the study's retrospective design precludes the provision of any data pertaining to the duration and behavior of CD, the type and duration of medications used, disease-free survival, or comprehensive molecular phenotypes.[11]

The challenging diagnosis

Since CD-associated SBA is often occult, imaging and endoscopy alone make it difficult to detect this pathology.[12,13] Studies showed that endoscopy and cross-sectional CT imaging for cancer screening in long-term CD patients had a sensitivity of 33%, which goes according to our case, since none of the tests carried out, namely CT, MRI and colonoscopy, raised the suspicion of malignant tumor of terminal ileum.[14] Recent retrospective review revealed that 90% of cases (total of 22 patients) were discovered incidentally on intraoperative frozen sections and/or postoperative final pathology, while only 9% (2 patients) were diagnosed preoperatively.[1] Besides, preoperative cross-sectional imaging missed moderately large tumors that later excised, as was our case (pT3).[1] This could most likely be explained by difficulty of distinguishing neoplasms and inflammatory alterations, which makes image-based diagnosis challenging. Another important aspect of this review article is fact that preoperative imaging did not detect small-volume peritoneal disease at index surgeries, which highlights CD-SBA cross-sectional imaging's limitations.[1]

Treatment

In early-stage disease with minimal and localized tumor burden, a biopsy for long-standing ileal strictures can be

inaccurate.[15] In these cases, surgeons should have a high index of suspicion for the diagnosis and try to get it preoperatively if possible. When unable to diagnose or faced with a high-risk phenotype intraoperatively, frozen sections should be explored. When it's not available like in our center, it's important to consider an oncologic mesenteric resection to optimize lymph nodes excision, with high mesenteric division, always keeping in mind the importance of small bowel preservation in CD patients.[1]

Most CD surgeries are cursed with restricted techniques and limited mesenteric resection, since its non-oncological context. Besides recent findings that extended mesenteric resection may prevent CD recurrence and increase lymph node excision, there must be a balance between the extended or oncologic mesenteric resection and the CD surgery's primary idea of bowel length preservation, especially after previous bowel resections.[16]

As for the lymphadenectomy, in our case we removed 35 lymph nodes, which goes according to the recommendations of other oncological studies that recommend the excision of a minimum of 12 lymph nodes for colorectal and small bowel cancer resections to evaluate node positivity.[17] In case of stage II patients with less than 12 lymph nodes excised, they should go under adjuvant chemotherapy (American Society of clinical oncology).[17,18] Therefore, in CD resections with a high index of suspicion for malignancy, surgeons should consider an oncological resection for curative-intent treatment and precise disease staging, if possible.[1] This method may prevent early-stage patients from receiving needless adjuvant chemotherapy if cancer is diagnosed later in a specimen with a low lymph node yield.

Overall survival

CD-SBA patients have poorer survival than those with de novo cancers due to disease rarity, low incidence, difficulties in preoperative diagnosis as previously discussed, and a lack of evidence on adjuvant chemotherapy in this context.[1] Indeed, prior studies revealed that adjuvant chemotherapy for CD-SBAs has limited efficacy, with response rates ranging from 22 to 42%.[18,19] Our case was discussed in the multidisciplinary team and it was decided to proceed with adjuvant systemic chemotherapy, taking into account the stage II (pT3N2M0) of the patient and 2 years later she remains recurrence-free. Greenstein et al and Michelassi et al found that only 9% of patients survived 2 years disease-free, with an overall survival of 8-44 months.[20] So, despite the latest advances in oncology, the survival rate in this subgroup of patients remains low.

Thus, long-standing CD patients should have the terminal ileum monitored regularly, and surgeons should be aware for occult SBA.

Surveillance

Post-resection patient surveillance mostly involves regular abdominal exams, serial surveillance, cross-sectional imaging, monitoring for obstructive symptom recurrence, and prompt investigations if new symptoms develop, especially after long quiescent periods.[20] Although in the present case the CEA has remained normal during the whole two years follow-up, the literature states that CEA monitoring has not been effective in SBA.

However, the evidence in this field is limited and more studies are needed to show how best to follow these patients.

CONCLUSION

There is a lack of clear guidelines for primary prevention and surveillance of SBA, except for emphasizing tight management of inflammation. It is wise to perform multiplanar imaging if the patient develops a symptomatic stricture after a long time without symptoms or if the stricture does not respond to medication. However, it should be noted that distinguishing between an inflammatory stricture and early-stage cancer is not always a straightforward task. Even with a greater understanding of the pathogenesis, preoperative SBA diagnosis techniques are scarce. Due to this and traditional Crohn's resections with limited mesenteric resection, patients remain at a risk of suboptimal treatment if an incidental cancer were to be found on histology. In this case, there were no pre- operative malignancy suspicions, so it was intraoperatively decided to perform an ileocolectomy. Although it was not an intentional oncological surgery, we were able to obtain a complete tumor resection and an adequate lymphadenectomy, which allowed a better posterior treatment orientation. The presented case of an SBA in a patient with CD emphasizes the importance of keeping a high level of suspicion of occult neoplasm in cases of long-standing CD, especially when associated with several episodes of intestinal occlusion (stenosing phenotype) and associated weight loss, including in patients under IMS, even when the pre-operative diagnostic tests do not point to the diagnosis of malignancy. A strategy may include a right mesenteric-based surgical technique that favors oncological principles of high-ligation and adequate lymph node dissection during the index surgery, or a frozen section and oncological resection if positive for cancer. Nevertheless, it´s crucial to keep in mind the importance of balancing optimal cancer treatment and bowel preservation in these patients, especially after previous bowel resections.

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