Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

Comment 1: First of all it should be clarified throughout the manuscript whether the paper deals with adenocarcinoma in the small intestine complicating Crohn´s disease or whether it deals with small intestinal adenocarcionomas in general. This is not obvious througout and much of the cited litterature does not deal with adenocarcinomas in Crohn´s disease. This is a very important point since the condition should be dealt with differently in the two cases. I would suggest that the introduction and the discussion should focus only on adenocarcinomas in Crohn´s disease as the case on which the paper is based deals with this matter. Not at least is this important since in the case of Crohn´s the diagnostic challenges can be immense while there is only one solution in patients not suffering from Crohns disease should an obstructive matter occur in the small intestine namely surgery.

Author's Response: **We would like to thank reviewer 1 for taking the time to review this manuscript and agree that it will be beneficial to further focus the content on CD-induced SBA. To do this we have eliminated: "Risk factors for SBA include hereditary mutations, celiac disease, and inflammatory bowel disease (IBD)" from the introduction to further focus the text on CD-induced SBA rather than sporadic SBA. We have also edited the portion of the introduction that details diagnostic and treatment methods to reflect that of CD-induced SBA.**

We have deleted the definition and incidence statistics pertaining to sporadic SBA in the first paragraph of the discussion: "SBA describes the malignant transformation of glandular epithelia and is the most prevalent malignancy of the types of small intestine cancers. The incidence of small bowel cancers in the US have risen from 1.18/100,000 in 19733 to 2.5/100,000 in 2021, and are 1.5 to 2 times more common in males than females". We have now also specified CD as the form of IBD that poses a great risk to the development of SBA in: "Known risk factors include consumption of alcohol, smoked foods and refined carbohydrates, a background of hereditary cancer syndromes including Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or inflammatory bowel disease (IBD), particularly CD[6]", before outlining statistics on the increased prevalence of SBA in CD patients, indicating CD-induced SBA as a characteristic entity. We have also now updated the statistic detailing 5-year survival rates of SBA to discuss CD-induced SBA specifically: "In light of this delay in diagnosis, CD-SBA has a markedly decreased 5-year survival rate at 20-30%[13] and increasing prevalence[14], as opposed to the 51.5% 5 year survival rate in CRC and decline in prevalence.[15]".

We have now changed the statistic regarding gender predisposition, to reflect CD-induced SBA specifically in the *Risk Factors* segment of our discussion: "CD-SBA is also three times more likely to affect males[2]", such that risk factors for sporadic SBA have been excluded.

We have also attempted to structure the proposed diagnostic methods outlined under the *Diagnostics* heading of our discussion to point towards novel applications in CD- induced SBA, despite none of the methods being prior used for this particular condition, as we suggest that they may be effective if attempted.

Under the *Survival and Effect of Biologics on Disease Progression* heading of our discussion we have eliminated data surrounding lymph node involvement and survival rates as they referred to sporadic SBA. We have now replaced that by discussing survivability and trends in outcomes of CD-induced SBA: "The mainstay of treatment for CD-SBA remains to be surgical resection of the primary tumor and loco-regional lymph node resection[3]. This may be accompanied with pancreatoduodectomy or right colectomy in the instances of lesions in the second and third portions of the duodenum or distal ileum, respectively[13]. The association between lymph node involvement and overall survival in CD-SBA is yet to be concretely studied, with very limited data[29,2,30,31]. CD-SBA carries a poor five year survival rate 3.7%, attributed to late diagnosis and ineffective treatment[2]. The usage of chemotherapy in CD-induced SBA is still not well studied and currently existing statistics only pertain to ampullary adenocarcinoma[2]."

Comment 2: History of past illness. It is somewhat shocking that the reason for not giving this severely ill Crohn´s patient the correct treatment during her long disease course which would have been biologics was due to cost restraints ! It should be noted at least in the discussion that early treatment with biologics could have changed the course of the disease.

Author's Response: **We would like to thank reviewer 1 and agree that this is important to note. We have now included: "Based on her prolonged duration of disease, we believe that early usage of biologics in the treatment of this patient may have altered the subsequent disease course." when discussing the potential merits of biologic treatment of CD-induced SBA under the *Survival and Effect of Biologics on Disease Progression* heading of our discussion.**

Comment 3: The incidence rates given is not the same as noted in the introduction. Which is correct ? It is stated that active surveillance for small bowel adenocarcinomas should be used i CD. Even though the condition is serious it is still rare in CD and no guidelines recommends surveillance. What is needed is the promp use of relevant diagnostics when the suspicion arises in individual patients.

Author's Response: **We would like to thank reviewer 1 for this comment. We have now removed those specific incidence rates as they had pertained to sporadic SBA. We had suggested that it would be a good idea to perform regular surveillance, as this condition poses a poor prognosis and it is always better to er on the side of caution, such that minimal cases go undetected before progressing to a state where it would be very difficult to treat. Furthermore, current statistics available regarding the survivability/ mortality of this condition are based off a very small population, potentially presenting skewed statistics, meaning that this condition could be more dangerous than we currently deem.**

Comment 4: It is noted that the actual patient did not fit into the typical demographics. I strongly disagree. The present patient had suffered from long lasting severe stricturing CD not treated optimally. She is a high risk patient.

Author's Response: **We completely agree with reviewer 1, CD-induced SBA was a differential for this patient as her symptoms were indicative of CD- induced SBA, the issue that arose was regarding the similarities between the symptoms of this condition and fibro stenotic CD. While her longstanding disease puts her at a high risk for this condition, the few studies that exist currently suggest that the target demographic include males and those at a younger age. We are suggesting that we must broaden our conceptualizations abut demographics and grow suspicious in instances of long standing disease: "She had also had a prior resection achieving surgical remission and a "reset" of prior inflammatory. Her symptoms at presentation were readily attributable to stricturing CD, signifying the need to broaden conceptualizations regarding demographic trends. – especially when risk factors such as prolonged duration of disease exist."**

Comment 5: The sensitivities and specificities given for MRE and CT in the detection of malignant lesions do not apply to detection of these lesions in stricturing Crohn´s disease.

Author's Response: **We would like to thank reviewer 1 for this comment. The provided statistics were for SBA in general, we have now updated the statement and statistic to reflect SBA in the setting of CD: "Currently CT and magnetic resonance (MR) enterography provide high specificity and sensitivity in the detection of stricturing malignant lesions of the small intestine; however, in the setting of CD, the accuracy of this modality in the detection of SBA is reduced to 47%[24] . Older contrast-based diagnostics such as enteroclysis require specific**

training, and fluorodeoxyglucose (FDG)-positron emission tomography (PET) also has a reduced accuracy in the setting of inflammation secondary to CD[2,25]"

Comment 6: Multidisciplinary care: As prevously noted I strongly disagree that the present patient is not by definition a risk patient for developing adenocarcionoma in the small bowel. Proposal of a novel algorithm: It is debateable whether DBE would be the method of choice if a suspicion of malignant transformation in a CD patient occurs. In such a patient there is a call for early surgery.

Author's Response: **We completely agree that it is debateable whether DBE would be beneficial in this setting, and thank reviewer 1 for bringing this up. However, based off the experience of Lee et al. who quickly diagnosed SBA prior to surgery very effectively, in conjunction with the high positive rate of diagnosis and ability of DBE to tangentially diagnose and deliver therapeutics, we suggest that this option may be beneficial in early diagnosis. However, we completely agree that early surgery would be required: "Furthermore, symptomatic strictures unresponsive to therapy should head to surgery early in the course of hospitalization".**

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors:

Comment 1: Strong recommendations:
The title, goal, and writing structure can be better adjusted. The manuscript was a mixture of case report and literature review with a review article. The freedom to discuss some points goes beyond the literary limit of the proposed design. We recommend a clear and explicit title as a case report and some review margins that are restricted to the subject you choose.
Example 1:
Title: "Confounding phenotypes: small bowel Adenocarcinoma in neoterminal ileum in setting of stricturing Crohn's disease – **Case report**".

Author's Response: **We would like to thank reviewer 2 for taking the time to review our manuscript, and providing insightful comments which will add strength to our paper. We**

definitely agree and believe that this would help clarify the type of content presented in the paper. We will now edit the title to be: "Confounding phenotypes: small bowel Adenocarcinoma in neoterminal ileum in setting of stricturing Crohn's disease: A Case report".

Comment 2: Example 2:
"We aim to highlight the future of CD-induced SBA management and discuss the potential merit of balloon enteroscopy and genetic testing for earlier detection." – **Were these methods applied in the case?** If the answer was not, we suggest change this aim.

Author's Response: **We would like to thank reviewer 2 for this comment. We agree that this poses confusion as we did not experience the efficacy of DBE, and now edit the sentence to be: "Here, we aim to highlight the future of CD-SBA management in the setting biologic therapy and propose one approach for early diagnosis."**

Comment 3: Example 3:
"The pathogenesis of CD-induced SBA suggests the prospect of genetic testing in refractory CD to investigate potential risk factors for malignancy development. Advances in liquid biopsy allow for the detection of tumor related markers through analysis of ctDNA, circulating free DNA (cfDNA) and circulating tumor derived endothelial cells (CTECs) in samples of biological fluids – **In this case, the same question can be done**. Were these methods applied in the case?

Author's Response: **We would like to thank reviewer 2 for this important comment. These methods were not applied in this case, and we completely agree that altering this statement will help emphasize this to be a suggestion from the experiences of other research groups rather than our own experience. We have now edited this to be: "The pathogenesis of CD-SBA highlights the potential for genetic testing in refractory CD to investigate potential risk factors for malignancy development. Zhou et al. demonstrated this potential through liquid biopsy that allow for the detection of tumor related markers through analysis of circulating tumor DNA (ctDNA), circulating free DNA (cfDNA) and circulating tumor derived endothelial cells (CTECs) in samples of biological fluids[19]."**

2. Minor recommendations:

Comment 4: The placement of the surgical specimen would be important.

Comment 5: Attention regarding the placement of acronyms with prior description (Ex: DBE)

Author's Response: **We would like to thank reviewer 2 for emphasizing this important point. We have now ensured that each acronym is properly described prior to usage.**

Comment 6: The proposal of a novel algorithm (LINE 240) could be deleted due to lack of scientific support. In this case is only an expert opinion.

Author's Response: **We would like to thank reviewer 2 for recommending this. We agree that it is difficult to propose a novel algorithm without a larger observational study to inform it. For this reason we would like to suggest our method as a potential approach that we believe would be beneficial based off our experience, and moreover as a topic that warrants a larger study to investigate.**