



Case report

Mucinous adenocarcinoma in perianal fistula in Crohn's disease: Case report and literature review

Ana Beatriz Pereira de Souza^a, Amanda Pereira Lima^a, Lívia Moreira Genaro^a,
Carla Peres Fingerhut Geiger^b, Maria de Lourdes Setsuko Ayrizono^a, Raquel Franco Leal^{a,*}

^a Colorectal Surgery Unit, School of Medical Sciences, University of Campinas, Campinas, São Paulo, Brazil

^b Department of Radiology, School of Medical Sciences, University of Campinas, Campinas, São Paulo, Brazil

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SUMMARY

Introduction and importance: Crohn's disease (CD) is a chronic bowel disease that, due to exacerbated inflammation, can lead to complications such as the development of perianal fistulas. The development of mucinous adenocarcinoma in perianal fistulas in patients with CD is rare and, consequently, few reports exist in the literature.

Case presentation: We report the case of a 71-year-old man diagnosed 22 years ago with CD with perineal involvement, who came with complaints of intense perianal pain, a gluteal mass, and local bleeding. Tomography of his abdomen showed an expansive, heterogeneous, and solid perianal mass on the right, with interspersed necrotic/liquefied areas and possible mucinous content. The patient was referred to the surgery department for an incisional biopsy, which confirmed mucinous adenocarcinoma. The patient underwent extra levator abdominoperineal rectal resection (APR) with partial proctectomy.

Clinical discussion: Perineal mucinous adenocarcinoma arising in a fistula associated with CD is very rare. Since the symptoms overlap, early diagnosis of malignancy is difficult. Histological analysis is the gold standard for its diagnosis. Surgical resection through APR is well-established and, despite being a complex procedure with potential complications, tends to have good results. However, the locoregional and inguinal lymph node involvement was related to a worse progression in this case.

Conclusion: The diagnostic hypothesis of mucinous adenocarcinoma should be suspected in CD patients who present long-term perineal involvement with fistulas. Biopsies and imaging exams should be performed to aid the diagnosis of the condition and thus contribute to the surgical plan.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (DII) whose etiology remains unknown and is characterized by periods of activity and remission. This disease presents with irregular and transmural lesions that can affect any part of the gastrointestinal tract, from the mouth to the anus [1]. Patients with CD may develop perianal lesions, such as skin tags, fissures, ulcers, abscesses, and fistulas [2]. In addition to the typical complications of the disease, CD is related to the occurrence of malignancy [3,4].

Colorectal cancer (CRC) has become a common disease in Western countries and accounts for approximately 10% of cancer-related deaths.

The main factors associated with this increase are population aging, poor eating habits, smoking, and obesity [5]. Mucinous adenocarcinoma is a subtype of colorectal cancer characterized by more than 50% of the tumor tissue being extracellular mucinous components [6]. The occurrence of mucinous adenocarcinoma in perianal fistulas of patients with CD is rare. The location of this type of tumor is extramucosal, that is, the tumor does not originate from the rectal mucosa, but the epithelium lining the perianal fistula internally. Thus, we report the case of mucinous adenocarcinoma in a perianal fistula of a CD patient.

Abbreviations: APR, abdominoperineal rectal resection; BMI, body mass index; CD, Crohn's disease; CRC, colorectal cancer.

* Corresponding author at: Colorectal Surgery Unit, Department of Surgery, School of Medical Sciences, University of Campinas, Carlos Chagas Street, 420, Cidade Universitária Zeferino Vaz, Campinas 13083-878, São Paulo, Brazil.

E-mail addresses: rafranco.unicamp@gmail.com, rafranco@unicamp.br (R.F. Leal).

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2. Methodology

This work has been reported in accordance with the SCARE Criteria 2020 [7]. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

3. Case presentation

A 71-year-old male patient, who was retired, started follow-up in the outpatient coloproctology clinic of the Clinic Hospital of the University of Campinas in December 2018, after being referred from an external center where he was diagnosed with perianal colorectal CD in 1999, without reports of previous surgeries. The patient's comorbidities were systemic arterial hypertension, congestive heart failure, chronic obstructive pulmonary disease (a former smoker of 35 packs of cigarettes/year), active alcohol consumption, and a history of pulmonary tuberculosis and hepatitis C, both of which were treated. Regarding CD, he did not complain of abdominal pain or diarrhea on evaluation and was in clinical remission (CD activity index value of 89). He had been started on infliximab (300 mg every four weeks) and azathioprine (150 mg per day) one year prior and had previously used sulfasalazine for 15 years. Because of his tuberculosis and hepatitis C history, anti-TNF α (anti-tumor necrosis factor α) was suspended until he was discharged from infectious diseases follow-up at the hospital. Magnetic resonance enteroscopy and colonoscopy were requested for the staging of the disease, which showed endoscopic remission. These colonoscopic findings are shown in Fig. 1.

The patient was lost to outpatient follow-up because of the new coronavirus pandemic. He self-presented again to the clinic in June 2021 complaining about intense perianal pain and a mass in the gluteal region with local bleeding. He denied losing weight, abdominal pain, or changes in bowel habits. He was only taking azathioprine and had not been using infliximab since having discontinued it in 2018. On physical examination, his body mass index was 21.64 kg/m², his abdomen was normal, and he had complex fistulas in the right perianal region, associated with a regional mass with ulceration and local phlogistic signs, besides fistulous orifices with spontaneous drainage of a serosanguineous secretion of gelatinous appearance (Fig. 2). Abdominal tomography revealed an expansive, heterogeneous, and solid perianal mass on the right, with infiltrative behavior and undefined borders, measuring 12.3 × 4.5 × 8.4 cm, with interspersed liquefactive necrotic areas (apparent mucinous content). Moreover, the exam showed an invasion of the perineal region and scrotum, anal canal, and pelvic floor muscles on the right. The mass contacted the apex of the prostate, without clear invasion. Lymphadenomegaly of the inguinal, external iliac, and bilateral obturator chains raised suspicion of secondary involvement, without evidence of distant metastases (Fig. 3). The patient was referred to the surgical center to undergo an incisional biopsy, which confirmed

the presence of mucinous adenocarcinoma.

Preoperative pelvic magnetic resonance imaging revealed a hyper signal in T2, suggesting mucinous adenocarcinoma (Fig. 4). Preoperative colonoscopy revealed that the CD was in remission. The indicated surgical approach was extra-elevator abdominoperineal rectal resection (APR) with partial prostatectomy, which was performed in September 2021 (Fig. 5). Histopathological and immunohistochemical analyses of the surgical specimen confirmed the hypothesis of mucinous adenocarcinoma arising in a perianal fistula and revealed tumor-free surgical margins (Fig. 6).

The patient remains under follow-up by the oncology and coloproctology teams, and was started on adjuvant treatment with Xeloda (60% dose). Azathioprine was suspended and the patient remains unmedicated for CD. Unfortunately, small lesions appeared in the remainder of the scrotal and inguinal regions, which suggested disease recurrence six months after surgery. The inguinal lymph nodes biopsy confirmed mucinous adenocarcinoma. The patient is receiving chemotherapy treatment as a palliative regimen.

4. Discussion

According to the Montreal classification, CD is subdivided into the inflammatory, stricturing, and penetrating phenotypes [8,9]. The presence of exacerbated inflammation, which is characteristic of CD, associated with transmural involvement of several layers of the intestine, may lead to the development of fistulas, especially in the perianal region. The symptoms include pain at the site and the presence of pus [10]. The risk of a patient with CD developing fistulas is between 21% and 23% throughout the disease course, and approximately 30% of CD patients are at risk of fistula recurrence [10–12]. Approximately 70% of patients with fistulas require surgical management [10].

Studies have shown the relationship between cancer and CD, including one by Jess et al. that investigated the risk of developing cancer in a cohort of 374 CD patients. They observed a 60-fold increase in the risk of CD patients developing small bowel adenocarcinoma compared to the general population [13].

Mucinous adenocarcinoma is a subtype of adenocarcinoma and is characterized by its proximity to the colon, a higher ratio of lymph node infiltration, and for being significantly larger [14,15]. The occurrence of mucinous adenocarcinoma in perianal fistulas is rare and is believed to be caused by dysplastic changes resulting from the constant regeneration of the fistular mucosa [16]. Some authors, including Ball et al., report that the use of immunosuppressant agents and anti-TNF medications may contribute to the appearance of this type of cancer [17], both of which are traditionally used for CD treatment.

The main reported complaints associated with mucinous adenocarcinoma are rectal bleeding, itching, secretion and/or abscess, pain, and presence of a large mass in the perineal region [18,19]. Because these

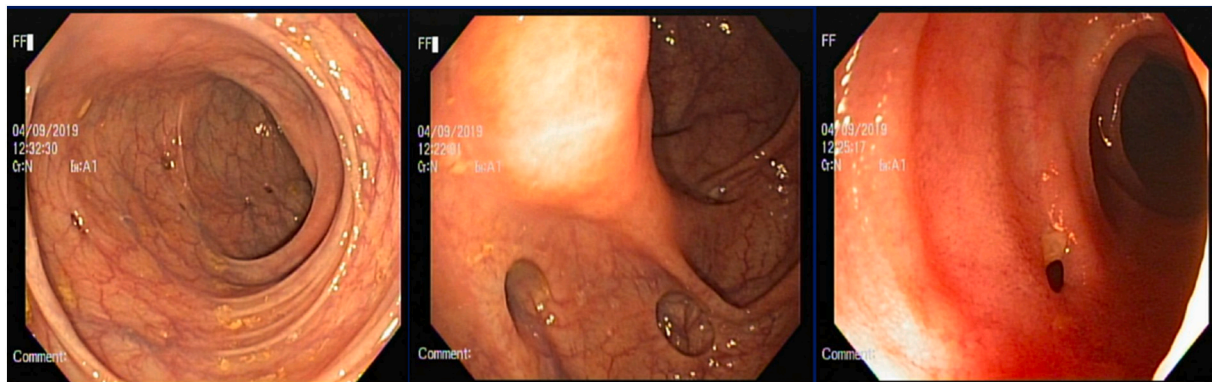


Fig. 1. Colonoscopy exam. Assessment of colonic segments with morphology, coloration, haustrations, and vascular network of normal endoscopic appearance. Rectum without changes. No signs of active inflammatory disease.



Fig. 2. Perineal fistula in a CD patient associated with malignant transformation to mucinous adenocarcinoma. Patient in the lithotomy position.

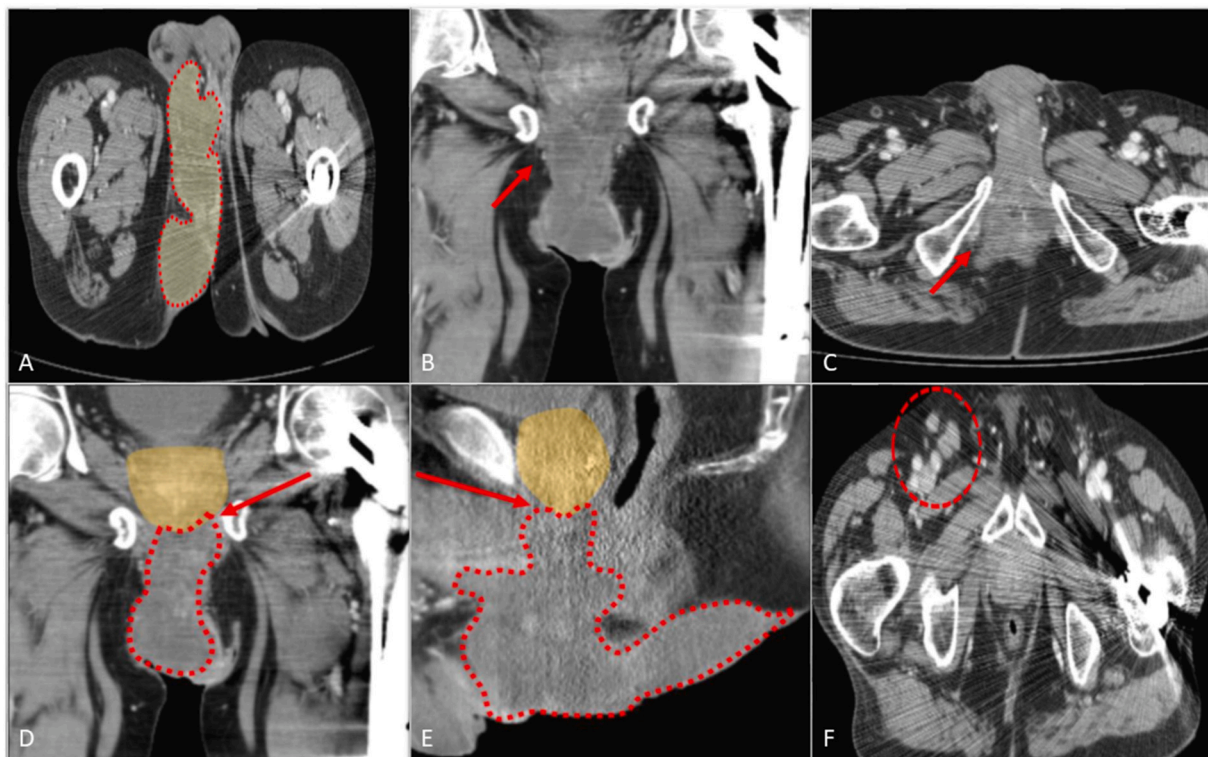


Fig. 3. Abdominal tomography shows an expansive, heterogeneous, and solid perianal mass on the right, with infiltration of the perineum and scrotum on the right (A), wide contact and no definition of the pelvic floor muscles (B, C), contact with the apex of the prostate (D, E), and suspicious inguinal lymph nodes (F).

symptoms are common in cases of benign fistulas, early diagnosis of malignancy is often hindered [20] and this delay may lead to an unfavorable outcome. The gold standard for diagnosis is the histological examination of the lesion, with confirmation obtained by the presence of extracellular mucinous pools or the finding of mucus accumulation in the cytoplasm [21–23]. Our histological identification of the biopsied

fistulous lesion confirmed the classic pattern of mucinous adenocarcinoma.

The literature describes a few cases of mucinous adenocarcinomas arising in perianal fistulas of CD patients. In a review performed by Sjö Dahl et al., the incidence of development of perianal mucinous adenocarcinoma was 0.7% in patients with CD [3]. Table 1 shows the

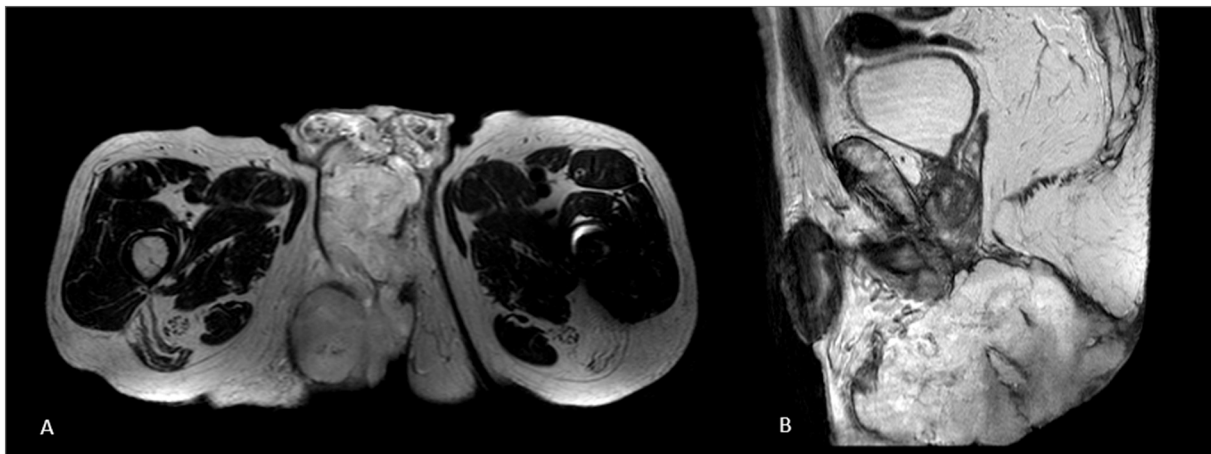


Fig. 4. Magnetic Resonance Image shows a hyper signal in T2, suggesting mucinous adenocarcinoma. (a) Transverse section (b) sagittal section.



Fig. 5. Extralevator abdominoperineal amputation of the rectum with partial prostatectomy (A, B). Perineal reconstruction (C).

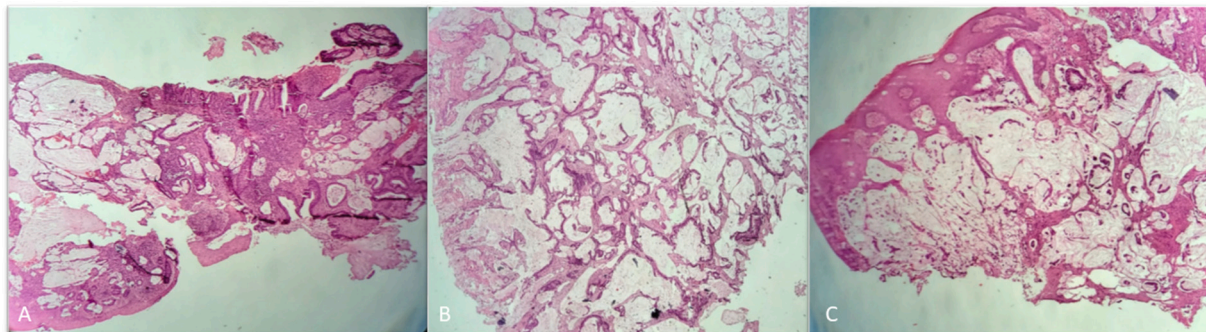


Fig. 6. Histological analysis: Adenocarcinoma with a mucinous pattern. (A, B, and C).

reports of cases published until now. The affected patients were aged between 18 and 79 years and the duration of CD varied between three and 33 years. The number of male patients exceeded that of female patients (14 and nine, respectively). All patients used some type of medication to treat CD. This had a direct effect on the modulation of the immune system, being either immunomodulators or anti-TNF biological agents, with the vast majority of patients using azathioprine and/or infliximab. The current patient exhibited the previously described characteristics in terms of sex, age, duration of CD, and previous use of immunosuppressant/anti-TNF medication.

Because of the malignancy of perianal mucinous adenocarcinoma, the indicated treatment for the disease is APR, and if the involvement of the circumferential margin is suspected or confirmed, the surgical margin should be extended to the extralevator component [24].

Subsequently, therapeutic follow-up with chemotherapy and radiotherapy is recommended [25].

APR with local excision of the perineal lesion is an acceptable treatment for cancer originating from perianal fistulas [26]. In the cases reported in the literature (Table 1), all patients underwent some type of surgical treatment aimed at controlling the disease. In four cases, exclusive surgical treatment was chosen, in eight chemo and/or radiotherapy was performed, and in one of the cases, radiotherapy treatment was used in a palliative way. The combination of chemoradiotherapy in the treatment of mucinous adenocarcinoma is not well established in the literature. Yang et al. suggest that chemoradiotherapy for mucinous adenocarcinoma from a perianal fistula is appropriate in cases where there is no total resection of the tumor or the patient refuses surgical treatment without evidence of distant metastasis [27].

Table 1
Occurrence of mucinous adenocarcinoma in CD patients– Cases reported in the scientific literature.

Author	Number of cases	Sex	Age (years)	CD	CD duration	Use of immunosuppressants	Use of anti-TNF	Metastasis	Treatment	Anatomopathological	Follow-up (months)
Keese et al. [28]	1	F	50	S	23	NR	NR	Yes	Pelvic Exenteration and sacral exeresis	Mucinous adenocarcinoma	NR
Cañete et al. [29]	1	M	51	S	32	NR	Infliximab	Yes	Pelvic Exenteration	Moderately differentiated mucinous adenocarcinoma	NR
De Alencar et al. [30]	1	M	43	S	3	NR	Infliximab	Yes	Abdominoperineal resection of the rectum, soft tissue exenteration, and chemoradiation	Invasive mucinous adenocarcinoma	2
Freeman et al. [31]	1	M	18	S	12	Azathioprine	Infliximab and Adalimumab	Yes	Loop colostomy and palliative radiotherapy	Mucinous adenocarcinoma	12
Melichar et al. [32]	1	M	39	S	21	Azathioprine and methotrexate	Infliximab	No	Abdominoperineal resection of the rectum and chemoradiation	Mucinous adenocarcinoma	8
Papaconstantinou et al. [33]	1	M	40	S	23	Azathioprine, methotrexate and mercaptopurine	Infliximab and Adalimumab	Yes	Abdominoperineal resection of the rectum and chemoradiation	Mucinous adenocarcinoma	3
Iesalnieks et al. [34]	6	4 M, 2 F	45,5*	S	26*	Azathioprine	No	Yes#	Abdominoperineal resection of the rectum and chemoradiation [#]	Mucinous adenocarcinoma	13 ^Ω
Smith et al. [35]	1	F	79	S	20	No	Infliximab	No	Abdominoperineal resection of the rectum with radical vulvectomy and perineum/vulva reconstruction	Well-differentiated invasive mucinous adenocarcinoma	NR
Scharl et al. [36]	1	F	45	S	25	Methotrexate and mercaptopurine	Infliximab, Certolizumab and Adalimumab	No	Rectal amputation and radiochemotherapy	Poorly differentiated mucinous adenocarcinoma	24
Inamdar et al. [3,37]	1	F	56	S	25	Azathioprine and mercaptopurine	No	No	Partial colectomy, followed by proctocolectomy, ileostomy, and tumor excision; Myocutaneous flap repair and chemotherapy + radiotherapy	Mucinous adenocarcinoma	15
Maejima et al. [35,38]	1	F	50	S	33	No	Infliximab	No	Abdominoperineal resection	Mucinous adenocarcinoma in the submucosa	18
Kim et al. [36,39]	7	5 M, 2 F	30*	S	13*	Azathioprine	Infliximab	NR	Abdominoperineal resection of the rectum ^Ω ; Total proctocolectomy ^δ ; Transanal excision ^δ ; Miles' surgery ^δ ; Therapy with concomitant chemoradiation [#] and chemotherapy ^φ	Mucinous adenocarcinoma	44*

NR: not reported; *: median; #: for five patients, Ω: for four patients; δ: for one patient; φ: for two patients.

In our review, in cases in which follow-up was performed, surgical treatment alone resulted in a survival of 18 months. In those in which chemoradiotherapy was associated, survival ranged between 2 and 44 months, and when palliative radiotherapy was used, 15 months. This may suggest that chemoradiotherapy is appropriate in the treatment of mucinous adenocarcinoma, but the analysis was impaired because only one of the four cases that underwent exclusive surgical treatment was followed up.

Because CD is a prevalent disease whose incidence has been increasing worldwide, its complications should be recognized to facilitate its early diagnosis, thereby reducing its morbidity/mortality. The development of mucinous adenocarcinoma in perianal fistulas of CD patients is rare. Therefore, reports of this condition are scarce. Thus, our study further clarifies this complication and contributes to its better understanding, despite how challenging its management is.

5. Conclusion

Our study aimed to present a rare case report of mucinous adenocarcinoma in a perianal fistula in a male patient with CD from a Brazilian tertiary service. Even though he was submitted to abdominoperineal resection of the rectum with partial prostatectomy, new lesions appeared, demonstrating recurrence of the disease. The patient remains in palliative cancer treatment. The occurrence of mucinous adenocarcinoma in perianal fistulas of CD patients is extremely rare. Few studies in the international literature describe this occurrence. Therefore, the objective of this report was to describe the progression, diagnosis, and management of this disease. Hopefully, this will eventually contribute to an earlier diagnosis. The combination of its rarity with its often non-specific symptoms hinders its early diagnosis. Its management involves a complex and extensive surgical procedure that is often associated with complications, depending on the degree of the lesion's extension. The presence of locoregional/inguinal lymphadenomegaly at presentation is a factor of poor prognosis.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

The case report was performed in accordance with the Clinical Hospital Ethical Committee of the University of Campinas, number 56605422.4.0000.5404.

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There was no funding for the research.

Author contribution

Ana Beatriz Pereira de Souza contributed to data collection and wrote the paper.

Amanda Pereira Lima contributed to data collection and helped in the writing of the manuscript.

Lívia Moreira Genaro helped in the writing of the manuscript.

Carla Peres Fingerhut Geiger contributed to the analysis of the radiological findings.

Maria de Lourdes Setsuko Ayrizono participated in the colorectal surgery and contributed to the final revision of the manuscript.

Raquel Franco Leal was enrolled in the supervision and conceptualization of the study; participated in the colorectal surgery and contributed to the final revision of the manuscript.

Guarantor

Raquel Franco Leal, MD, PhD.

Registration of research studies

Not applicable.

This study is a case report.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors have nothing to disclose and personal relationships.

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