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Peritoneal Mesothelioma in a Patient with Long-Standing Crohn's Disease: Cause or Coincidence?

Rita Prata[a] Pedro Lages Martins[a] Verónica P. Borges[a] Pedro Botelho[b] António Figueiredo[c] Jaime Ramos[a]

[a]Department of Gastroenterology, Unidade Local de Saúde de São José, Lisbon, Portugal; [b]Department of Colorectal Surgery, Unidade Local de Saúde de São José, Lisbon, Portugal; [c]Department of Pathology, Unidade Local de Saúde de São José, Lisbon, Portugal

Keywords
Peritoneal mesothelioma · Crohn's disease · Chronic inflammation

Abstract
Introduction: Peritoneal mesothelioma (PeM) is a rare cancer of the peritoneal lining. Unlike pleural mesothelioma, PeM is less frequently linked to asbestos exposure. Chronic serosal inflammation, as seen in Crohn's disease (CD), has been proposed as a contributing factor in its carcinogenesis. ***Case Presentation:*** A male with a long-standing history of ileal CD presented with recurrent episodes of intestinal subocclusion. Imaging showed complex active ileal CD, new-onset ascites, and peritoneal densification. Intraoperatively, a small bowel mass adherent to the sigmoid colon and millimetric nodules of the peritoneum were identified. Histology of the resected segment showed CD-related changes and multiple areas of epithelioid mesothelioma, despite no asbestos exposure. He received cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, with no signs of recurrence after 15 months. ***Discussion/Conclusion:*** We present a rare case of non-asbestos-related PeM in a patient with long-standing active CD, highlighting the diagnostic challenges and possible link between chronic serosal inflammation and PeM.

Mesotelioma peritoneal em doença de Crohn de longa duração: causa ou coincidência?

Palavras Chave
Mesotelioma peritoneal · Doença de Crohn · Inflamação crónica

Resumo
Introdução: O mesotelioma peritoneal (PeM) é uma neoplasia primária rara do revestimento peritoneal. Ao contrário do mesotelioma pleural, o PeM está menos frequentemente associado à exposição a amianto. A inflamação serosa crónica, como a que se pode observar na doença de Crohn (DC), tem sido proposta como um fator que contribui para a carcinogénese do PeM. ***Apresentação do caso:*** Homem com diagnóstico de DC ileal de longa evolução apresentou-se com episódios

karger@karger.com
www.karger.com/pjg

Correspondence to:
Rita Prata, mprata.rita@gmail.com

recorrentes de suboclusão intestinal. Imagiologicamente, exibia alterações sugestivas de DC ileal complexa ativa, e ascite e densificação peritoneal de novo. No intraoperatório, foi identificada uma massa do intestino delgado aderente ao cólon sigmoide e nódulos milimétricos do peritoneu. A histologia do segmento ressecado mostrou alterações compatíveis com DC e múltiplos focos de mesotelioma epitelióide, apesar da ausência de história de exposição a amianto. Foi submetido a cirurgia citorredutora combinada com quimioterapia intraperitoneal hipertérmica, sem evidência de recidiva após 15 meses de seguimento. ***Discussão/Conclusão:*** Apresenta-se um caso raro de PeM não relacionado com exposição a amianto num doente com DC ativa de longa duração, destacando os desafios diagnósticos e a possível ligação entre a inflamação serosa crónica e o PeM.

Introduction

Peritoneal mesothelioma (PeM) is a rare malignancy arising from the mesothelial cells that line the peritoneal cavity [1]. Environmental or occupational contact with asbestos is the most well-established risk factor. However, unlike pleural mesothelioma, PeM is less frequently linked to asbestos exposure [2]. The pathogenesis of PeM likely involves complex genetic and molecular mechanisms, and chronic serosal inflammation – such as that seen in patients with Crohn's disease (CD) – has been postulated as a contributing factor in PeM carcinogenesis [3]. Here, we present a case of PeM in a patient with a long-standing history of Crohn's disease with no documented asbestos exposure.

Case Report

A 46-year-old man with a history of long-standing stricturing and fistulizing ileal CD presented to our clinic with a 6-month history of recurrent episodes of intestinal subocclusion. He was first diagnosed at 19 years old after undergoing a diagnostic workup for recurrent abdominal pain and diarrhea, achieving clinical remission with steroid therapy. Five years later, he experienced a relapse with steroid dependency and was started on azathioprine. Twelve years post-diagnosis, the patient developed a perianal fistula, which was successfully treated with adalimumab (ADA) administered every other week, resulting in complete fistula closure. A decade later, the ADA dosage was optimized to weekly administration due to a relapse with abdominal cramps, vomiting, and diarrhea. While clinical improvement was noted, imaging showed persistent complex active ileal CD with transmural inflammation, serosal adhesions, stricture, and fistula formation.

At the current presentation, he reported no additional symptoms. Both physical examination and blood workup were unremarkable, with therapeutic ADA levels (8.9 μg/mL) and low fecal calprotectin (71 μg/g). Computed tomography (CT) enterography revealed significant thickening of the distal ileum wall with adhesive and fistulizing changes to the sigmoid colon, as well as new-onset ascites and peritoneal densification (Fig. 1), with no pathologic lymph nodes. After a multidisciplinary team (MDT) meeting and case review, surgical intervention was proposed due to the significant worsening of obstructive symptoms and the inability to definitively exclude a neoplastic complication, such as small bowel adenocarcinoma. Complementary chest CT showed no abnormalities. The patient had undergone a surveillance colonoscopy under deep sedation 6 months earlier, which identified a recess compatible with an internal fistula opening 20 cm from the anus. However, it was not possible to reach the right colon due to fixation, and no other mucosal abnormalities were detected. Since CT enterography identified pathological changes confined to the small bowel, with no additional colonic involvement beyond ileo-sigmoidal fistulization, it was concluded that repeating an ileocolonoscopy would offer no additional benefit as it would not alter the surgical indication.

Intraoperatively, a small bowel mass adherent to the sigmoid colon, millimetric nodules of the peritoneum, and ascites were identified. The procedure involved adhesiolysis, aspiration of abdominal fluid, ileocecal resection of 30 cm of bowel, and extraction and closure of the ileosigmoid fistula. The procedure and the postoperative period were uneventful. Histopathologic analysis of the resected stenotic segment revealed changes consistent with CD, without evidence of dysplasia. Additionally, multiple foci of epithelioid mesothelioma were identified in the small bowel serosa (Fig. 2a). These lesions exhibited a tubulopapillary pattern, invading the intestinal wall up to the muscularis propria, with immunohistochemical staining positive for calretinin (Fig. 2b) and CK7 and negative for CK20.

The patient had no history of asbestos exposure. Following MDT discussion and staging of the PeM, he underwent concurrent cytoreductive surgery – including total omentectomy, peritonectomy, anterior rectum

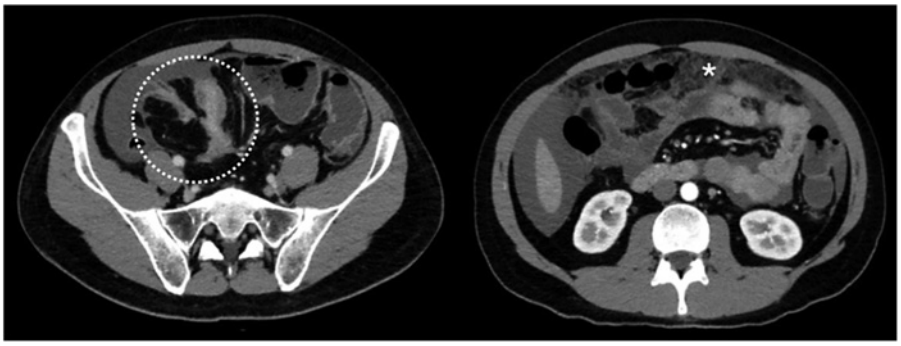

Fig. 1. CT enterography showing significant thickening of the ileal wall with adhesive and fistulizing changes to the sigmoid colon (dotted white circle), ascites, and peritoneal densification (white asterisk).

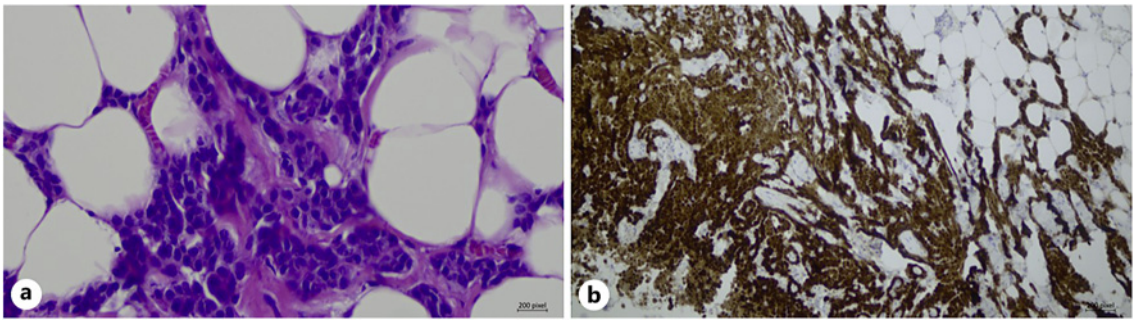

Fig. 2. a Epithelioid mesothelioma with a solid and papillary pattern invading the adipose tissue. **b** Cells were positive for calretinin (hematoxylin-eosin stain (**a**); calretinin stain (**b**), original magnifications, ×200).

resection, and cholecystectomy – combined with hyperthermic intraoperative peritoneal perfusion with chemotherapy. At the 15-month follow-up, the patient remains asymptomatic with no signs of recurrence and is under close monitoring.

Discussion

PeM is a rare and aggressive cancer of the peritoneal lining, with incidence rates in industrialized countries estimated at 0.2–3 cases per million [1]. Pleural mesothelioma, the most common type, accounts for approximately 80% of all mesothelioma cases, while PeM comprises only 15–20% [2].

Mesothelioma is closely associated with chronic inflammation, particularly in the context of asbestos exposure. Asbestos fibers are known to induce a chronic inflammatory response and oxidative stress, leading to DNA damage in mesothelial cells [4].

The carcinogenesis of PeM is complex, multifactorial, and still poorly understood. Compared to pleural mesothelioma, PeM is less frequently associated with asbestos exposure, and many cases are considered idiopathic. While asbestos exposure is still the most significant risk factor, it is present in only about 33–50% of cases of PeM, compared to over 90% in pleural mesothelioma [3]. Other non-asbestos-related causes of PeM include genetic factors, such as germline mutations in the BRCA1-associated protein-1 (BAP1) gene, and other environmental exposures, though these account for a small proportion of cases [1, 5].

Moreover, chronic inflammation has been implicated as a risk factor in cases of non-asbestos-related PeM, suggesting that persistent serosal inflammatory states may play a role in its pathogenesis [3, 5]. This aligns with the broader understanding that chronic inflammatory states can contribute to carcinogenesis, potentially through mechanisms involving persistent cellular damage and repair. Patients with CD, a chronic inflammatory disorder characterized by inflammation of all layers of the intestinal wall and involvement of the mesentery [6, 7], are at increased risk of developing small bowel and colorectal cancer [8, 9].

To the best of our knowledge, only 3 cases of PeM arising in patients with CD have been reported in the

Table 1. PeM cases in patients with CD reported in the literature

Reference	Age	Gender	Diagnosis of CD duration	Imaging features	PeM type	Survival	Asbestos exposure
Butnor et al. [10]	60	Female	40 years	Small bowel wall thickening	Epithelial	30 months	No
Butnor et al. [10]	65	Female	3 years (long history of prior diarrhea)	Regional enteritis with small bowel obstruction	Biphasic	2 months	No
Butnor et al. [10]	56	Male	>20 years	Terminal ileum narrowing and omental nodules	Epithelial	Alive with disease after 30 months	Potential occupational exposure as a brake worker

CD, Crohn's disease; PeM, peritoneal mesothelioma.

Table 2. Differential diagnosis of PeM

Differential diagnosis
IBD-related stricture/inflammation[a]
Peritoneal carcinomatosis
Small bowel adenocarcinoma
Primary small intestinal lymphoma
Intestinal tuberculosis
Reactive mesothelial hyperplasia
Serous peritoneal carcinoma
Lymphomatosis
Eosinophilic enteritis
Amyloidosis
Sarcoidosis

[a]In the setting of prior IBD diagnosis.

literature (Table 1). Butnor et al. [10] reviewed approximately 3,800 cases of mesothelioma, including 500 cases of PeM, and identified 3 patients with both PeM and a prior diagnosis of CD. In all cases, CD had been diagnosed at least 3 years (ranging from 3 to 40 years) before the diagnosis of PeM. In the case with the shortest duration of established CD, the patient had a long history of prior diarrhea. Potential occupational exposure to asbestos was documented in only 1 case [10].

Remarkably, no cases of PeM have been reported in patients with ulcerative colitis, which supports a potential link between PeM and the transmural inflammation, and consequent serosal inflammation, seen in CD. There is evidence that adipocyte progenitors in the mesenteric adipose tissue of CD, the «creeping fat», exhibit increased mesothelial characteristics, which may contribute to the chronic inflammatory environment, potentially influencing mesothelial cell behavior and proliferation [11]. Wilkinson et al. [12] described a case of an exuberant mesothelial reaction in longstanding CD ileitis mimicking malignant mesothelioma, highlighting the diagnostic challenges in differentiating between benign mesothelial proliferation and malignant mesothelioma in the context of CD. Furthermore, chronic serosal inflammation from other conditions, such as familial Mediterranean fever [13], endometriosis [14, 15], and long-standing intra-abdominal catheters [16], has been described as a risk factor for PeM, supporting the potential role of chronic inflammation in mesothelial carcinogenesis.

Clinically, the disease typically progresses within the peritoneal cavity, often manifesting with nonspecific symptoms such as abdominal pain, distension, and ascites, which can contribute to delayed diagnosis and worse prognosis [2, 3]. This is particularly challenging in patients with longstanding CD due to overlapping clinical and imaging features that may be misinterpreted as an exacerbation or nonresponse to medical therapy. Table 2 summarizes the main differential diagnoses to consider. CT imaging of the abdomen and pelvis is the recommended diagnostic tool for preoperative assessment [17]. In this case, the true significance of the new-onset ascites and peritoneal lining densification was initially underestimated, even though the importance of excluding a neoplastic complication was addressed at the MDT meeting.

Similar to pleural mesothelioma, the histologic subtypes of PeM include epithelioid (about 60% of cases of all cases), sarcomatoid (around 20%), and biphasic (approximately 20%) [18]. The main prognostic factors

include the histologic subtype – with epithelioid histology associated with a better prognosis – lymph node involvement, and the completeness of cytoreduction [17, 19]. Regardless of etiology, for selected patients with diffuse PeM, no extraperitoneal disease spread, good performance status, and a high likelihood of achieving complete surgical cytoreduction, cytoreductive surgery with hyperthermic intraoperative peritoneal perfusion with chemotherapy is the cornerstone of treatment and significantly improves survival [20]. Studies have demonstrated a median survival of 29.5–92 months and a 5-year survival rate of 39–63% with this approach [18, 19]. For patients who are not candidates for surgery or have recurrent disease, multiple intravenous systemic therapy options are available and are primarily based on clinical trials conducted in patients with pleural mesothelioma. In this context, immunotherapy, either alone or in combination with chemotherapy, has emerged as a significant treatment modality for PeM [19, 20].

This case report presents a rare case of non-asbestos-related PeM in a patient with long-standing active complex ileal CD. Overall, the rarity of PeM limits our understanding of its epidemiological features. There is evidence suggesting a link between chronic serosal inflammation – as illustrated in this case – and PeM. However, the precise mechanisms and clinical significance of this relationship are still unclear, and it is not possible to infer a cause-effect association. Further research is needed to better understand this relationship.

Statement of Ethics

Ethics approval was not required for this study in accordance with local/national guidelines. Informed consent was obtained from the patient for the publication of this article and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors made substantial contributions to the article. Rita Prata drafted the manuscript. Pedro Lages Martins, Verónica P. Borges, Pedro Botelho, António Figueiredo, and Jaime Ramos critically revised the manuscript. All the authors approved the final version of the manuscript.

Data Availability Statement

The complete data of this study are not publicly available due to the patient's privacy but are available from the corresponding author upon reasonable request.

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