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Sarcoidosis Mimetizing a Metastatic Colorectal Cancer Disease: A Case Report and Literature Review

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Abstract

The association between colorectal cancer and sarcoidosis exists, but it is not well documented. We present a case from a female patient, diagnosed with a rectal cancer, wich in the staging exams showed thoracic and cervical lymph nodes suspicious for metastatic disease. After we consider the low volume of disease at the pelvis, we decide to performed a lymph node biopsy, that showed sarcoidosis at the thoracic lymph nodes and locally-advanced disease in the rectum. The patient performed chemorradiotherapy and was submitted to curative surgery from the cancer. She also treated the sarcoidosis with corticosteroids, and now she is in clinical follow-up, without evidence of cancer disease.

Keywords: sarcoidosis, colorectal cancer, lymphadenopathy

Introduction

Sarcoidosis is a non-infectious granulomatous disease that especially affects young adults. Although of unknown etiology, it is believed to develop due to an abnormal host immune response to an unknown antigen in genetically susceptible individuals **[**1,2**]**. Colorectal cancer (CRC) is a frequent disease, with approximately 150,000 new cases annually in the United States, approximately 30% of which are tumors of the rectum3. The association between sarcoidosis and cancer is still controversial, but it has been described in the literature.

Case Presentation

Female patient, white, 49 years old, obese, coronary artery disease, hypertensive and social alcoholic. She started with sporadic hematochezia about 1 year ago. Due to the COVID-19 pandemic, medical care was postponed until September 2020, when episodes of hematochezia became more frequent. On that occasion, anoscopy showed a lesion 2 cm from the anal border. She continued investigation with colonoscopy, which identified an ulcerative-vegetative lesion in the distal rectum, whose anatomopathological examination showed adenocarcinoma. On staging Positon emission tomography scan (PET-CT), prominent lymph nodes were found in level III cervical, mediastinal and bilateral hilar chains, with a relatively symmetrical distribution, in addition to tenuous peripheral micronodules in the apicoposterior segment of the left upper lung lobe, raising the possibility of secondary lesions or sarcoidosis as a differential diagnosis (Fig.1).

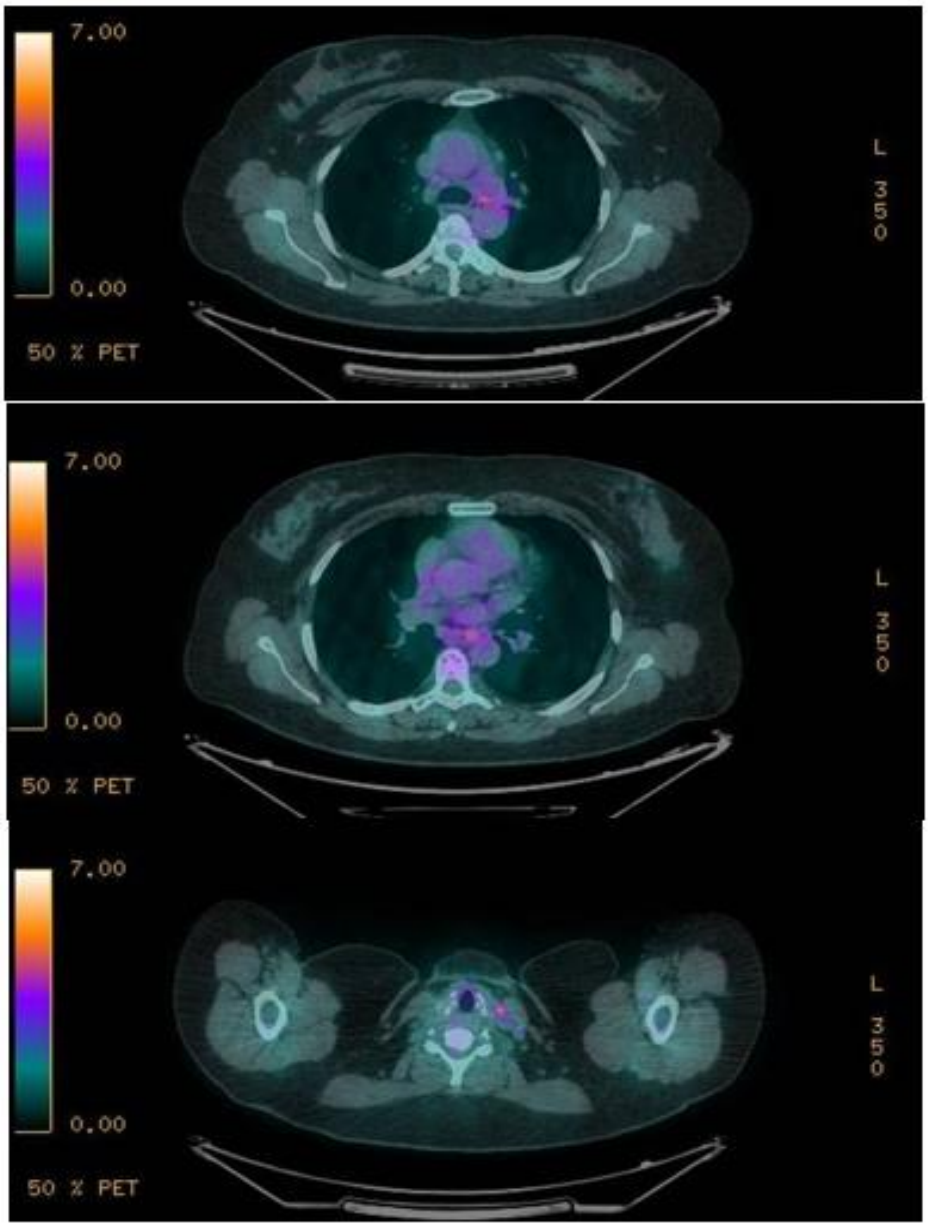

Figure 1 - PET-CT images showing prominent lymph nodes in mediastinal and cervical level III

The patient underwent an excisional biopsy of the cervical lymph node, whose anatomopathological examination revealed that it was chronic non-necrotizing granulomatous lymphadenitis with the presence of multinucleated giant cells, some of which had rare asteroid-like elements, which was compatible with sarcoidosis (Fig 2; Fig 3).

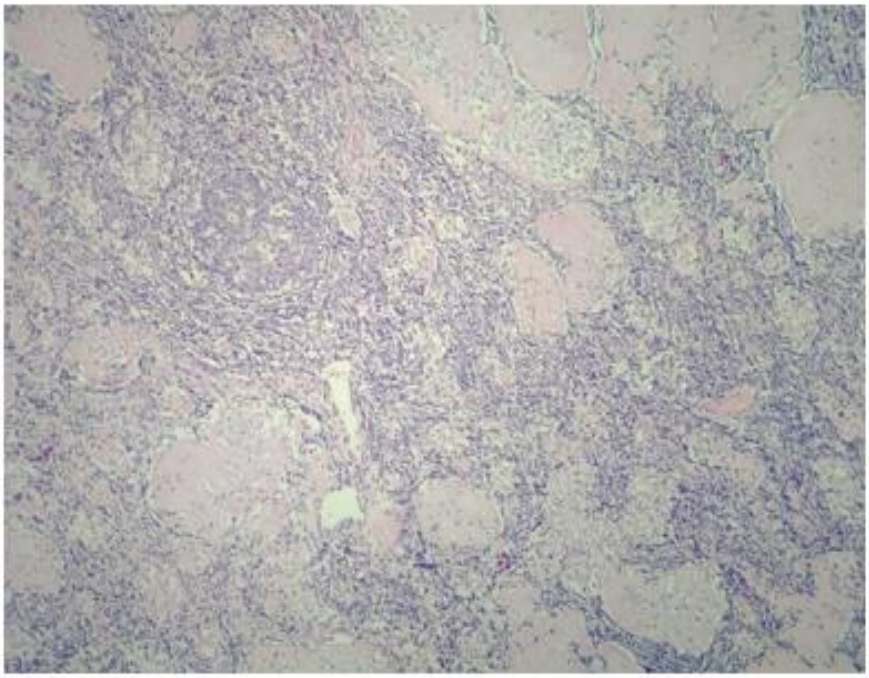

Figure 2. 40x magnification. Lymphoid tissue with multiple granulomas with hyalinization, without necrosi

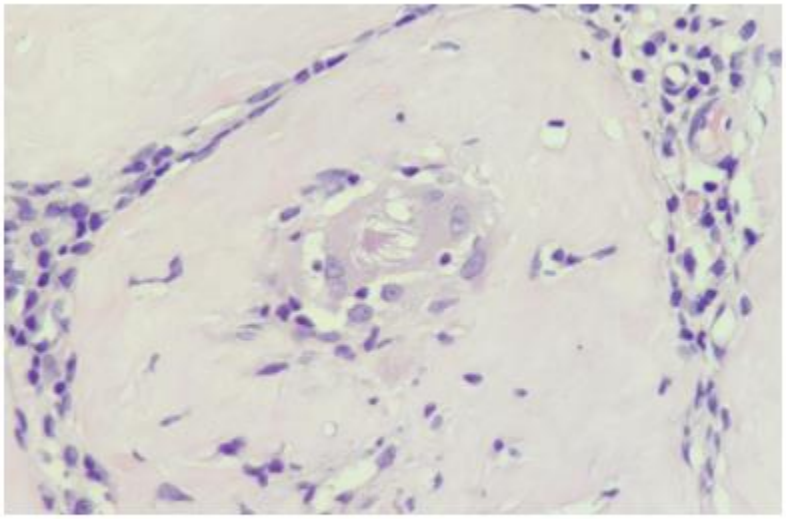

Figure 3 - 400x magnification. Granuloma with multinucleated giant cell, in the center with eosinophilic structure (asteroid body)

After that, it was then classified as Stage III (cT2cN1M0), and treatment with neoadjuvant chemoradiotherapy (capecitabine and IMRT 27 frations - 2Gy per fraction) was indicated, in addition to corticosteroid therapy for sarcoidosis. After neoadjuvant therapy and adequate treatment of sarcoidosis, the new CT scans showed complete remission of the previously described pulmonary and lymph node findings. Following oncological planning, she underwent rectosigmoidectomy in April 2021, with ypT3ypN0 staging, with no evidence of disease after surgery, and adjuvant FOLFOX was proposed. The patient did not present any signs or symptoms of systemic sarcoidosis and remains clinically well, with no signs of recurrence so far.

Discussion

The increase in the frequency and severity of the sarcoidosis disease in black patients reinforces the role of genetic factors; the single nucleotide polymorphism (rs2076530 G-A) of the butyrophyllin-like 2 (BTNL2) gene was considered an independent risk factor for sarcoidosis, probably influencing the activation and regulation of T2 lymphocytes. Sarcoidosis is histologically characterized by the presence of non-necrotizing granulomas rich in macrophages and T lymphocytes, especially CD4+, and asteroid bodies may be present **[**4,5**]**. Of uncertain prevalence, it is estimated from 10 to 20 cases per 100,000 people, the incidence varies between geographic regions, being 3 to 4 times more common in black Americans and in women, with most diagnoses between the second and fourth decades of life1. In fifty percent of the cases, presents with bilateral, symmetrical hilar or mediastinal adenopathy. Pulmonary reticular opacities and lesions in the skin, joints and/or eyes, with pulmonary disease being the most prevalent presentation (90%) **[**6,7**]**. The most common symptoms are cough, enlarged lymph nodes, erythema nodosum, fatigue and low-grade fever.

Some authors suggest a difference between sarcoidosis and sarcoid reactions, a definition that is still controversial8. The diagnosis of sarcoidosis requires three main conditions: compatible clinical or radiological presentation, evidence of granulomas in a biopsy sample and exclusion of differential diagnoses9. In turn, the sarcoid reaction is generally defined as a non-caseating granulomatous reaction, which does not meet the diagnostic criteria for sarcoidosis **[**10,11**]**. Ariish et al. suggest that they are the same entity, with the same findings on imaging and histology, which is our perception in this report **[**10,12**]**.

Although CRC mortality has been decreasing, it is still the third leading cause of cancer death in women and the second in men, with an increasing incidenc e among people under 50 years of age. Approximately 20% of patients are metastatic at diagnosis. The dissemination of RCC occurs via the lymphatic or hematogenous route, and in tumors of the distal rectum, drainage is through the inferior rectal vein, which drains into the inferior vena cava instead of the portal venous system, and may initially metastasize to the lungs instead of to the liver **[**13**]**.

The first proposition of a possible relationship between sarcoidosis and malignancy is dated from 1972, by Brincker **[**2**]**. Sarcoid granulomas are uncommon pathological findings in cancer patients, however, several patients have been identified with the development of sarcoidosis during or after cancer, suggesting its causal association with malignancy **[**14,12**]**. The finding of sarcoid reactions in cancer patients can occur in up to 4 % to 14% of patients **[**10**]**. These reactions have been well described in patients with lymphoma and various solid organ malignancies, including lung cancer, breast cancer, colorectal cancer, and genitourinary cancer **[**14**]**. In the literature, there are still few reports describing an association between sarcoid-like reactions and colon cancer; in a retrospective study, Grados et al. identified 12 patients who developed sarcoidosis after diagnosis of solid neoplasms, especially after breast and colorectal cancer **[**15**]**. Herron et al. evaluated 289 patients with oncological disease; 17.3% had a simultaneous diagnosis of sarcoidosis, the most common malignancy being those of the gastrointestinal tract (20%), and all patients had suspicious radiological findings for metastasis, but with confirmation of sarcoidosis in the biopsy16; of the patients with colorectal adenocarcinoma, all had findings consistent with pulmonary sarcoidosis and lymph node involvement. While pulmonary metastases are more commonly observed in rectal neoplasms, they observed that pulmonary sarcoidosis occurred independently of tumor venous drainage **[**15**]**. Some authors also suggest the possibility of developing sarcoid reactions related to certain types of chemotherapy, such as oxaliplatin-based regimens **[**17**]**.

Many studies have shown an increased risk of cancer in patients with sarcoidosis; a systematic review with a cohort of more than 25,000 patients showed a significant, albeit moderate, relationship between the two diseases, with an Relative Risk (RR) of 1.19 (95% CI, 1.07-1.32) for the development of neoplasms in patients with sarcoidosis, especially lymphoproliferative diseases, but also showed a significantly increased risk for some solid organ neoplasms, such as colorectal cancer, with an RR of 1.33 (95% CI, 1.07-1.67) **[**18**]**.

However, other studies have shown better survival in patients with a diagnosis of cancer and a finding of sarcoidosis. O'Connell suggests the presence of sarcoid granulomas to represent the expression of their host's systemic response to the tumor, with the possibility of enjoying longer remissions and better survival, independent of the stage of the disease19. In a study of patients with non-small lung cancer, sarcoid reactions were observed in 4.3%. None of them had granulomatous diseases; lymph nodes that exhibit granulomatous reactions do not combine with metastatic involvement, suggesting that this may be a prognostic marker, indicating absence of metastases **[**20**]**. Typically, sarcoid reactions involve regional lymph nodes of the organ of origin of the tumor, however, distant lymph node involvement may be associated with less metastatic difficulties and survival; the presence of granuloma was associated with a lower incidence of metastatic disease (OR = 0.195, 95% CI 0.073–0.521, p = 0.001) and better survival rates at 2, 4, 6 and 10 years, in a retrospective study **[**21**]**.

More studies are needed to understand the protective mechanism involved, however, it is believed that the occurrence of sarcoid reactions in cancer patients indicates a robust individual immune response to circulating tumor neoantigens, which may be a marker of good prognosis [19,20,22,23]. This effect is probably due to a complex immunopathological response mediated by T cells, considering the possibility that tumor cells are prevented from evading activated immune cells in those microenvironments where there is a high rate of granuloma formation, with consequent inhibition of tumor growth secondary to the immune reaction in patients with neoplasia [15,24,25]. Evidence that sarcoid reactions can appear at distant sites from the origin of stress supports the hypothesis that they must develop from an immune response involving T cells10. Further investigation of this proposition may lead to new therapeutic cancer immunotherapy agents.

With the disseminated use of PET-CT for cancer staging, there has been an increase in the frequency of detection of sarcoidosis [25]. Differential diagnosis between metastasis and sarcoid reactions, however, is not easy using only imaging tests, such as CT or PET-CT [27,28]. On PET-CT, there is the possibility that a benign lymph node with inflammatory activity has a high SUV, which is a false-positive result that would simulate malignancy [29]; compared to malignant lymph nodes, lymph nodes affected by sarcoidosis tend to be larger than 1 cm, bilateral and smaller in number30, however, to date, no SUV value on PET-CT has been defined as a cut-off point to distinguish between benign or malignant28. PET-CT can help in the monitoring of sarcoidosis, as it assesses disease activity and guides therapeutic choices, but it cannot be considered the most important procedure for the diagnosis of the disease [31]. Despite the characteristic increase in lymph nodes associated with sarcoidosis, during oncological follow-up, the evidence of a PET-CT detecting an increased uptake of mediastinal lymph nodes requires biopsy of these nodes to confirm the diagnosis, and the discussion with the pathologist is of paramount importance to increase the sensitivity of the diagnosis, including the possibility of complementary immunohistochemical staining, if necessary [8].

Cases of sarcoidosis related to colorectal cancer are still rare in the literature, which makes it difficult to assess the causal relationship between the diseases [30]. Additional studies focusing on the clinical significance and prognostic value of this relationship are needed [23]. During oncological follow-up, the presence of pulmonary nodules or mediastinal lymph nodes suspected for metastases always require histological confirmation, as sarcoidosis is considered a great mimic and this can affect the oncological therapeutic decision. Sarcoidosis continues to be a challenge, both due to the clinical picture and the evolution and response to therapy, remaining a diagnosis of exclusion [30].

We discuss here the case of a patient diagnosed with rectal adenocarcinoma and suspicious findings of pulmonary micronodules and mediastinal and hilar lymphadenopathy in staging tests prior to the start of treatment. Due to the histological evidence of a simultaneous diagnosis of sarcoidosis and cancer of the rectum, the patient can be adequately treated with a curative intent, as opposed to the possibility of being undertreated, if she were wrongly classified as having a metastatic disease by the exclusive

evaluation of the imaging tests, which would directly influence their prognosis. This reinforces the importance of making a pathological diagnosis whenever possible in patients with suspected metastatic disease.

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