

Review Article

Secondary Mesenteric Panniculitis as a Paraneoplastic Syndrome: An Updated Review

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Abstract: In response to the case of a patient with mesenteric panniculitis (MP) and proliferative disease, we reviewed the literature on their possible association and associations with other neoplasms. MP is a non-specific chronic inflammation of the mesenteric fat, with low prevalence and unknown etiology; patients may be asymptomatic or present predominantly gastrointestinal complaints. The disease can be either primary or secondary to other pathologies, including neoplastic ones. Diagnosis is made via computed tomography (CT) and confirmed by biopsy. Currently, there is no established treatment for MP. The literature contains series of variable sample sizes, case reports, reviews of other published studies, and some series after a 5-year follow-up. Papers tend to be relatively consistent when it comes to prevalence data and clinical manifestations. However, there is still controversy regarding the role that secondary MP could play in a paraneoplastic picture. From the diagnostic point of view, the incorporation and use of positron emission tomography (PET), together with CT, has been helpful for the approach and the diagnostic focus in this field. Nevertheless, its usage and the discrimination cut point between inflammatory pathology and tumor pathology (maximum standard uptake value: SUVmax) are not clearly defined in neoplastic cases.

Keywords: Mesenteric Panniculitis, Abdominal Mass, Paraneoplastic Phenomenon, CT, PET/CT

1. Introduction

Mesenteric panniculitis is a rare entity that encompasses

everything from chronic, non-specific inflammation of the mesentery to its fibrosis and necrosis. The disease has been called “mesenteric sclerosis” when the dominant feature is fibrosis, “mesenteric panniculitis” when it is inflammation,

and “mesenteric lipodystrophy” when it is fat necrosis. Other terms used in the medical literature include: retractile mesenteritis, sclerosing mesenteritis, xanthogranulomatous mesenteritis, mesenteric lipogranuloma, liposclerotic mesenteritis, isolated lipodystrophy, and retroperitoneal xanthogranulomatosis [1]. First described by Jura *et al.* in 1924 [2] as retractile mesenteritis, only in 1965 did Ogden *et al.* [3] coin the term mesenteric panniculitis.

The epidemiology is somewhat uncertain, with reported prevalence ranging from 0.16% to 7.83% due to the variability of the criteria used [1]. The disease presents most frequently in white men (ratio men: women 2:1) [4, 1], and its appearance increases with age (mean age 62 years) [1]. The rising use of imaging techniques has also positively impacted the number of cases described.

The clinical spectrum varies from cases with few or no symptoms, diagnosed incidentally (10%), to those with severe manifestations, with the most frequent symptom being abdominal pain (70%) [5]. Other signs may include a palpable mass, fever, nausea, vomiting, diarrhea or weight loss, which can be related to the inflammation and/or the mass effect [6]. One way or another, one of its main characteristics is variability, with some cases appearing as a latent condition with a long-term evolution (especially in primary cases) and others having a fatal outcome (secondary cases) or even spontaneous recurrences [7].

The pathogenesis seems to involve a non-specific response to a wide variety of stimuli that affect the mesentery of the small intestine, the mesoappendix, the sigmoid colon, and the intra-abdominal fatty tissue [8]. Its exact etiology is unknown [4], but it could be present in a primary form or be associated in a secondary way to other comorbidities or behaviors like tobacco use; processes preceding abdominal surgery (3.3%); abdominal trauma (0.9%); auto-immune diseases such as those related to immunoglobulin (Ig) G4, intestinal inflammatory disease, systemic erythematous lupus, Behcet's disease, and sarcoidosis, among others (2.8%). Infectious diseases (e.g. tuberculosis, syphilis) or neoplasms (26%) are also potential factors, especially non-Hodgkin's lymphoma (NHL) and to a lesser extent colorectal cancer and bladder-prostate cancer [1, 4].

With regard to diagnosis, non-specific alterations may appear on blood tests, such as an increase in the erythrocyte sedimentation rate in 16.5% of patients, or anemia in 15.6% [1], but diagnosis usually relies on imaging studies such as abdominal ultrasound, with abdominal CT standing out as the most sensitive and least invasive method. This test shows changes such as hyperattenuation of the mesenteric fat, calcifications and retroperitoneal lymphadenopathies, the fat halo sign, and a tumorous pseudocapsule [5]. Another imaging technique is the PET-CT, with very high specificity, used especially in patients in whom the MP is suspected to be secondary to a neoplasm; this test can help select and direct clinicians to the area needing biopsy. Finally, the gold standard for diagnostic confirmation is biopsy [1].

There is no consensus about the right treatment for MP; the literature describes numerous medical as well as surgical

options. Asymptomatic forms may not require treatment at all (as there have been cases of spontaneous remittance) but only outpatient monitoring. Surgery is indicated in cases with complications such as obstruction, diagnostic suspicion of neoplasms (as an alternative diagnostic method to image-guided biopsy) or if there is a predominance of fibrosis with associated local complications. Pharmacological treatment may be used to address symptoms when these are mild (e.g. analgesia), although glucocorticoids are the cornerstone treatment in cases with a strong inflammatory component, as these are associated with a better response and prognosis [5]. When the MP is secondary, treatment is directed at the primary associated pathology (the autoimmune, neoplastic, infectious or inflammatory disease).

2. Case Information

A 75-year-old woman presented after 24 hours of nausea and visceral abdominal pain stemming from the left iliac fossa. She did not show any alterations in bowel movements, fever, or urinary or respiratory symptoms. The only notable finding from blood tests was a C-reactive protein level of 6.09mg/dL (reference range 0 to 0.5), with normal results in terms of the erythrocyte sedimentation rate, biochemical parameters, immunoglobulins, and tumor biomarkers (including β 2-microglobulin). The abdominal and pelvic computed tomography (CT) revealed clustered mesenteric adenopathies, the largest of which measured about 3 cm, with accumulation of the pseudoencapsulated fat surrounding them, compatible with mesenteric panniculitis. Positron emission tomography (PET) showed two large adenopathies/hypermatabolic conglomerates measuring 30 mm by 16 mm, and a maximum standardized uptake value (SUVmax) of 13.22mCi. The result of the ultrasound-guided core needle biopsy was CD20+ low grade follicular lymphoma (2008 World Health Organization classification), while the Tru-Cut biopsy of the bone marrow showed paratrabeular and interstitial infiltration by the follicular lymphoma. The final diagnosis was CD20+ stage IV (bone marrow) non-Hodgkin's (follicular) lymphoma, associated with mesenteric panniculitis. Is mesenteric panniculitis related to the presence of neoplasms?

3. Results

The main radiological patterns obtained by CT described in the literature are collected in the Figure 1 Well-defined fatty mass at the root of the mesentery, hyperattenuation of the fatty mass, lymph nodes inside this well-defined fatty mass, hypodense halo surrounding the blood vessels and nodes (“fat halo sign”), and hyperdense pseudocapsule delineating the lesion.

Legends: a) Well-defined fatty mass at the root of the mesentery, displacing neighboring structures; b) Hyperattenuation of the fatty mass, higher than that of retroperitoneal or subcutaneous adipose tissue; c) Lymph nodes inside this well-defined fatty mass; d) Hypodense halo

surrounding the blood vessels and nodes, or the “fat halo sign”; and e) Hyperdense pseudocapsule delineating the lesion.

We have reviewed the most important or relevant papers

published, focusing on the possible association between MP and neoplasms. These studies are summarized in Table 1.

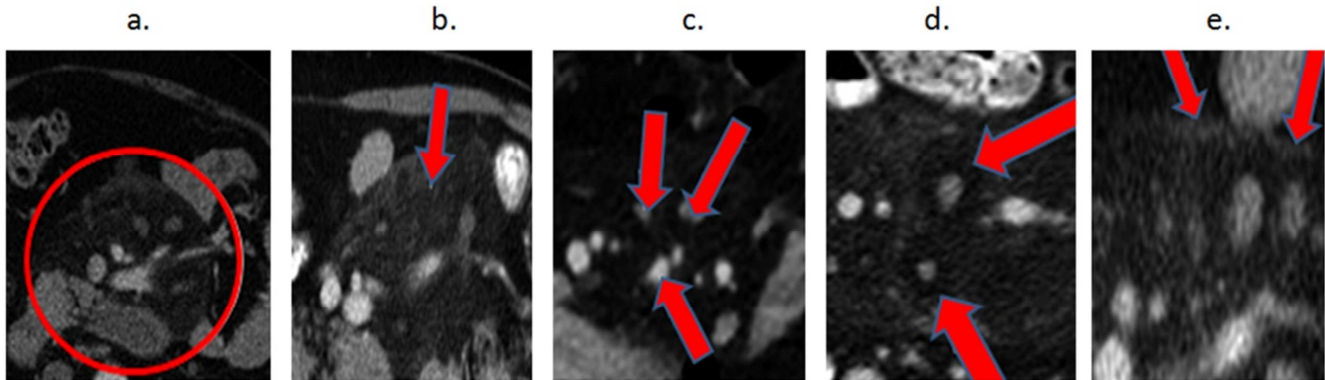


Figure 1. Images and radiological characteristics of mesenteric panniculitis on computed tomography, as described in the literature [9].

Table 1. Characteristics of main studies of MP [4, 10-19].

Study	
Methods and aims	Findings and conclusions
Mesenteric panniculitis. Odgen et al., 1965 [3]	
Review of 27 cases of MP.	2 patients developed lymphoma and 1, mesenteric fibrosis. Although the MP may have a favorable evolution, the physiopathological mechanism is still unclear.
Mesenteric lipodystrophy. Kipfer et al., 1974 [10]	
One of the first studies testing the association between MP and malignancy.	
Diagnosis via laparotomy.	
CT evaluation of mesenteric panniculitis: prevalence and associated diseases. Daskalogiannaki et al., 2000 [11]	
Prospective study with 7620 abdominal CTs.	MP presents as a diffuse mesenteric thickening (42%), a single discrete tumor (32%), or multiple tumors (26%). Coexistence with lymphoma: 15%.
Primary aim: assess the prevalence of MP and associated diseases.	
Mesenteric panniculitis in oncologic patients: PET-CT findings. Zissin R et al., 2006 [22]	
Retrospective study: review of 33 PET-CT scans in 19 cancer patients.	MP is observed on CT in 49 patients (0.6%), of which 34 (69.4%) had a malignancy—frequently NHL (n = 6)—and 11, benign tumors.
Aim: to assess PET-CT for its role in differentiating between MP and MP coexisting with tumors. FDG uptake in mesenteric nodes was measured.	Classifies patients as: - Group A: increased mesenteric uptake (n = 8) - Group B: no mesenteric uptake (n = 11) 7/8 patients in group A presented MP with tumor (6 lymphoma and 1 recurrent cervical carcinoma).
Normal positron emission tomography-computerized tomogram in a patient with apparent mesenteric panniculitis: biopsy is still the answer. Ehrenpreis E et al., 2009 [23]	
Case report and analysis of PET-CT results in the diagnosis of MP	Patient with chylous ascites. The PET-CT did not show FDG uptake in the mesentery or lymph nodes suspected of malignancy. Exploratory laparoscopy showed thickening of the mesenteric fat. Biopsy diagnosis of NHL.
Multidetector-row computed tomography findings of sclerosing mesenteritis with associated diseases and its prevalence. Canyigit et al., 2011 [12]	
Retrospective study in 2100 patients between 2007 and 2009.	The most important possible causal factors associated with MP were: malignancy (17.6%), previous surgery (33.3%), tobacco use (39.2%), coronary disease (17.6%), urolithiasis (19.6%), hypertension (35.2%), hyperlipidemia (25.5%), and diabetes mellitus (21.5%).
Primary aim: to describe CT findings and assess prevalence of associated diseases.	
Mesenteric panniculitis. Prevalence and natural course. MDCT prospective study. Courlier B et al., 2011 [20]	
Selection of characteristic images of MP on CT (5-year study period).	The main radiological signs of MP on CT are presented, along with the principal entities in the differential diagnosis of MP.
Literature review and differential diagnosis.	Conclusion: PET-CT is useful for ruling out mesenteric tumor involvement in patients with typical MP.
Mesenteric panniculitis: a paraneoplastic phenomenon? Wilkes et al., 2012 [13]	
Retrospective, single-center study analyzing clinical records and images.	Neoplasms in 45 patients (38%), most frequently colorectal cancer, lymphoma, and tumors of the urogenital tract.
Primary aim: to assess the prevalence of malignancy in patients with MP.	Conclusion: identifying MP on imaging tests can alert physicians to the possibility of associated malignant tumors.
Is mesenteric panniculitis truly a paraneoplastic phenomenon? A matched pair analysis. Gögebakan et al., 2013 [16]	
First case-control study (77 cases /152 controls).	Prevalence of MP: 0.58%.
Primary aim: re-evaluate the association between MP and malignancy.	50.6% of patients with MP had a coexisting malignancy, versus 60.2% of controls (p = 0.157).
Matching by year of CT, CT protocol, sex, age, and waist circumference.	Conclusion: MP is not a paraneoplastic phenomenon nor is it associated with other entities.

Study	
Methods and aims	Findings and conclusions
Mesenteric panniculitis: prevalence, clinicoradiological presentation and 5-year follow-up. Van Putte-Katier et al., 2014 [17]	
Retrospective study, evaluating 3820 CTs in a search for MP. Primary aim: assess the prevalence of MP along with these patients' clinico-radiological characteristics and outcomes. Follow-up: 5 years.	Prevalence of MP = 2.5%. Typical radiological characteristics: higher density of mesenteric fat, fat halo sign, and small soft tissue nodes. Coexistence of MP with malignant neoplasm (especially prostate carcinoma): 48.9%. During 5-year follow-up, patients with MP developed more malignant tumors (14.6%) than controls (6.9%).
Malignancy and mesenteric panniculitis. Cross et al., 2015 [14]	
Prospective study in 259 patients diagnosed with MP by CT. Aims: to identify the frequency and types of neoplasms associated with MP and assess the diagnostic role of CT.	Relation with malignancy: 30%. Conclusion: in cases where both entities coexist, the most frequent primary tumor sites are the large intestine, lymph nodes, and the urogenital tract.
Mesenteric panniculitis: systematic review of cross-sectional imaging findings and risk of subsequent malignancy. Halligan et al., 2016 [15]	
Systematic review of 14 studies. Primary aim: to assess any association between the imaging characteristics of MP and associated neoplasia.	Study heterogeneity. Conclusion: there are no available studies that determine an association between MP and malignancy.
Mesenteric panniculitis (MP) in CT – a predictor of malignancy? Scheer et al., 2016 [4]	
Retrospective study. Primary aim: assess the relationship between MP and malignancy. Malignant: non-malignant 107:36.	Prevalence of PM = 2.5%. In the group of patients with cancer, the prevalence of MP is 5.42%, significantly higher ($p < 0.005$) than in patients with no oncological disease. MP was more prevalent in cases of NHL (22.6%). Conclusion: MP is associated with a 5-fold higher risk of tumor disease ($p < 0.001$).
Mesenteric panniculitis: review of consecutive abdominal MDCT examinations with a matched-pair analysis. Protin-Catteau et al., 2016 [18]	
Retrospective study, evaluating 3054 CT scans to identify 96 cases with MP and 192 age- and sex-matched controls. Primary aim: assess the prevalence of MP and its relationship with neoplasia. Follow-up: 5 years.	Prevalence of PM = 3.14%. Malignant pathology: 60.4% in MP group and 59.4% of controls ($p = 0.86$). Conclusion: no significant differences between groups for the appearance of new neoplasms ($p = 0.15$).
Is there an association between mesenteric panniculitis and lymphoma? A case control analysis. Khasminsky et al., 2017 [19]	
Retrospective study of NHL and MP, using imaging tests (CT and PET-CT). Primary aim: to assess the prevalence and associations of MP in patients with NHL and controls (166:332).	Prevalence of MP in patients with NHL: 1.8%, corresponding to the range of prevalence observed in the general population ($p > 0.05$). Conclusion: MP is not related to NHL.

CT: computed tomography; MP: mesenteric panniculitis; NHL: non-Hodgkin's lymphoma; PET: positron emission tomography.

4. Discussion

The cause of MP is uncertain and subject to some debate. Different authors have described a variety of associated comorbidities, mostly in isolated cases or small, uncontrolled series. Some studies have reported an association between MP and malignancy, most of them speculating that it could be a paraneoplastic phenomenon [10-15]. However, it is still difficult to discern the direction of the causal pathway, if it even exists. There is a strong suspicion that MP is associated with lymphoma, although the reported prevalence varies considerably, from 7.8% to 33% [9].

In 1974, Kipfer et al. [10] noted the appearance of malignant tumors in 32.3% of patients with MP, and years later Daskalogiannaki et al. [11] corroborated these findings with an even higher rate (69.4%). In two other studies, the proportion of neoplasms in patients with MP was 17.6% (Canyigit et al. [12]) and 38% (Wilkes et al. [13]). Cross et al. [14] included 259 patients with MP, but just 30% of these had cancer. In 2016, Halligan et al. [15] performed a systematic review of 14 studies, finding a mean rate of malignancy of 38% in patients with MP.

In recent years, controlled studies have been performed with the primary aim of assessing the possible interactions between MP and other comorbidities, with a special focus on paraneoplastic phenomena [4, 16-19]. In 2013, Gögebakan et al. [16] carried out the first case-control study in 77 patients

with MP and 152 controls matched for the year of CT, CT protocol, sex, age, and waist circumference. The researchers observed malignancies in 50.6% of the cases and 61.2% of the controls, concluding that MP was not a paraneoplastic phenomenon but was rather associated with other diseases.

A year later, a second study with a similar design (Van Putte-Katier et al. [17]) observed that MP was significantly associated with malignant neoplasms in general and with prostate carcinoma in particular. The rate of malignancy was 48.9% in the MP group versus 46.3% in the controls ($p < 0.05$). Moreover, the number of malignant tumors increased significantly more during follow-up in the MP group ($p < 0.05$). The results of this study were criticized because of errors in the analysis and interpretation of the results, so it failed to firmly establish an association between prostate carcinoma and MP.

In 2016, Scheer et al. [4] published a retrospective study investigating a similar hypothesis as the previous ones. The authors confirmed the association between malignant neoplasms and MP, estimating an incidence of malignant tumors of 74.8% in patients with MP (compared to 35.2% in the general population), with an especially high prevalence of NHL (22.6%).

However, in Protin-Catteau et al.'s study [18], the percentage of patients with malignant neoplasms was not significantly different among cases (60.4%) and controls (59.4%), except for lymphoma and melanoma. Similarly, over

the course of the five-year follow-up, the cases did not exhibit a higher prevalence of neoplasms. The authors could likewise not verify the association between MP and other comorbidities like hypertension, diabetes, diverticulitis, and tobacco use.

In a 2017 study [19], Khasminsky et al.'s primary aim was to assess the association between MP and NHL in 166 patients with NHL and 332 age- and sex-matched controls. PET-CT scans showed a prevalence of MP of 1.8% in the NHL group, similar to the 2.1% rate seen in the control group ($p = 0.56$), leading investigators to conclude that MP and NHL were not associated.

Regarding diagnosis, many cases of MP are detected incidentally in the context of a CT performed for another reason. In most of these cases, diagnostic confirmation via biopsy does not take place. Furthermore, diagnosis is not always subject to the same radiological criteria. Scoring systems do exist, like the one proposed by Coulier et al. [20], and some research groups accept these because they help to standardize the signs of MP and allow comparison between studies. However, they are not typically used in daily clinical practice because the scores are not correlated with clinical symptoms, and they are of limited value in terms of clinical relevance, future complications, and the need for treatment. This system requires the presence of at least three of five signs (Figure 1).

Some authors have proposed [^{18}F] fludeoxyglucose (FDG) PET-CT as a secondary diagnostic tool when there is a suspected association between MP and an oncological pathology, to differentiate between malignant and benign associated pathologies [21]. However, PET is seldom used to diagnose secondary MP, and the SUVmax values indicating its presence are variable in the literature, even with cutoffs that are currently considered low (SUVmax $< 3\text{mCi}$ in the case of rectal adenocarcinoma with MP and an SUVmax of 2.72mCi) [21]. The available literature is still scarce and contains discrepancies. Zissin et al. [22] concluded that a negative PET has high diagnostic accuracy, as it rules out mesenteric tumor involvement, while the increased uptake suggests the coexistence of mesenteric deposits, particularly in patients with lymphoma. Ehrenpreis et al. [23] argue that PET examination is not advisable in patients with MP-like findings on CT, and that only biopsy is capable of excluding tumor involvement. Moreover, on suspicion of MP secondary to a neoplasm, the gold standard diagnosis is based on ultrasound-guided biopsy, as performed in our patient. In other cases, it is necessary to schedule a surgical lymph node biopsy [24]. In our opinion, the PET offers relevant information with respect to the best biopsy site and helps to maximize diagnostic yield, as it delineates the lymph node regions with the highest uptake, which are the most suitable for making an accurate diagnosis of the associated neoplasm.

All of the studies reviewed have limitations and carry some risk of specific bias, complicating the extrapolation of the results. The main included studies are summarized in table 1.

5. Conclusion

The literature review arising from our clinical case did not

yield any clear recommendations or guidelines regarding the right diagnostic approach to MP. There is little information about the relationship between secondary MP and other, mainly neoplastic, entities. Most studies do not contribute sufficient evidence, and there is substantial heterogeneity and variability between them, with important differences in diagnostic criteria and imaging techniques. Thus, there is still controversy around the association between MP and malignancy.

6. Recommendations

Defining, establishing, and formulating a diagnostic and treatment algorithm that can be implemented in daily clinical practice—which today is still indeterminate and non-standardized—is essential for formulating new research hypotheses and forming collaborative working groups.

Author Contributions

Each author (MGF, MDJR, PEA, JMM, AMJ, SCP, FCH, CSP, MSP, LRU, CGC, JMNC, DBT, SBE, PRR, JPG, APF, JMSR) certifies that she/he has made a direct and substantial contribution to the work reported in the manuscript by participating in each of the following three areas: (1) conceiving and designing the study; or collecting the data; or analyzing and interpreting the data; (2) writing the manuscript or providing critical revisions that are important for the intellectual content; and (3) approving the final version of the manuscript.

Conflicts of Interest

None of the authors have personal conflict of interest nor have they received payments for the performance of this work.

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