

## Lupus mastitis in men

Mastite lúpica em homens

Mastitis lúpica en hombres

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### **Abstract**

To analyze the pathophysiological aspects of lupus mastitis (LM), clinical presentation, epidemiology, radiological and histological findings, and treatment, to disseminate it to the academic community and draw attention to this pathology as one of the differential diagnoses in the management of breast lesions in males, especially in the case of breast cancer in men. A literature review was done by searching scientific studies in the PubMed / Medline, Scopus, Scielo, Embase, Web of Science, and Google Scholar databases. Relevant scientifically validated studies related to lupus mastitis in men were selected. The analysis, review and selection of articles carried out in pairs, blindly and separately, based on the reading of the title and abstract, with a third reviewer in case of disagreement. The LM should be suspect in patients known to have lupus erythematosus who present painful breast nodules associated with skin changes. However, LM can be the initial manifestation of lupus and mimic, both clinically and imaging, malignant neoplasms. The histopathological diagnostic criteria are well-established, finding mainly hyaline fat necrosis and lymphoplasmacytic infiltrate. Treatment must be drug-based as invasive procedures can exacerbate the injury. Due to physiological and anatomical aspects, this condition can appear and evolve differently in men. The knowledge of this pathology is necessary to carry out the correct approach since the non-identification of the disease and its erroneous management can lead to complications and irreversible sequelae to the patient.

**Keywords:** Mastitis; Lupus erythematosus panniculitis; Breast diseases; Male breast neoplasms; Male breast tumors; Men's health.

## Resumo

Analisar os aspectos fisiopatológicos da mastite lúpica (ML), apresentação clínica, epidemiologia, achados radiológicos e histológicos, e tratamento, no intuito de difundir perante a comunidade acadêmica e chamar a atenção desta patologia como um dos diagnósticos diferenciais na abordagem de lesões mamárias no sexo masculino, sobretudo em se tratando do câncer mamário em homens. Realizou-se pesquisa e revisão de literatura nas bases de dados PubMed/Medline, Scopus, Scielo, Embase, Web of Science e Google Scholar. Selecionou-se estudos relevantes, cientificamente validados, relacionados à mastite lúpica em homens. A análise, revisão e seleção dos artigos foi feita por pares, de forma cega e separada, a partir da leitura do título e resumo, havendo um terceiro revisor em caso de discordância. A ML deve ser investigada em pacientes sabidamente portadores de lúpus eritematoso que apresentam nódulos mamários dolorosos associados a alterações cutâneas. Porém, a ML pode ser a manifestação inicial do lúpus e mimetizar, clínica e imagiologicamente, neoplasias malignas. Os critérios diagnósticos histopatológicos são bem estabelecidos, encontrando principalmente necrose gordurosa hialina e infiltrado linfoplasmocitário. O tratamento deve ser medicamentoso, dado que procedimentos invasivos são capazes de exacerbar a lesão. Devido a aspectos fisiológicos e anatômicos, esta afecção pode surgir e evoluir de forma distinta em homens. O conhecimento desta patologia é necessário para realizar a abordagem correta, uma vez que a não identificação da doença e o seu manejo errôneo podem propiciar complicações e sequelas irreversíveis ao paciente.

**Palavras-chave:** Mastite; Paniculite de lúpus eritematoso; Doenças mamárias; Neoplasias da mama masculina; Tumores da mama masculina; Saúde do homem.

## Resumen

Analizar los aspectos fisiopatológicos de la mastitis lúpica (ML), presentación clínica, epidemiología, hallazgos radiológicos e histológicos y tratamiento, con el fin de difundirlo a la comunidad académica y llamar la atención sobre esta patología como uno de los diagnósticos diferenciales de las lesiones mamarias en los hombres, especialmente en el caso del cáncer de mama. Se realizó una revisión de la literatura mediante la búsqueda de estudios científicos en las bases de datos PubMed / Medline, Scopus, Scielo, Embase, Web of Science y Google Scholar. Se seleccionaron estudios relevantes y científicamente validados relacionados con la ML en hombres. El análisis, revisión y selección de artículos se realizó por parejas, a ciegas y por separado, en base a la lectura del título y el resumen, con un tercer revisor en caso de desacuerdo. Debe investigarse ML en pacientes con lupus eritematoso conocido que presenten nódulos mamarios dolorosos asociados con cambios en la piel. Sin embargo, la ML puede ser la manifestación inicial del lupus y simular cánceres, tanto clínica como por imágenes. Criterios de diagnóstico histopatológico están bien establecidos, encontrando principalmente necrosis grasa hialina e infiltrado linfoplasmocítico. Tratamiento debe basarse en medicamentos, ya que los procedimientos invasivos pueden agravar la lesión. Debido a aspectos fisiológicos y anatómicos, esta condición puede aparecer y evolucionar de manera diferente en los hombres. El conocimiento de esta patología es necesario para realizar el abordaje correcto, ya que la no identificación y su manejo erróneo pueden derivar en complicaciones y secuelas irreversibles.

**Palabras clave:** Mastitis; Paniculitis de lupus eritematoso; Enfermedades de la mama; Neoplasias de la mama masculina; Tumores de la mama masculina; Salud del hombre.

## 1. Introduction

Lupus panniculitis or lupus profundus is a rare presentation of systemic lupus erythematosus (SLE) or discoid lupus erythematosus (DLE), which affects about 2-3% of lupus patients and is more associated with the discoid form (Arsenovic & Terzic, 2008).

It is the subcutaneous tissue acute or chronic inflammation promoted by the lupus autoimmune action (Kinonen *et al.*, 2010). The first description was from Kaposi (1883), who reported the presence of subcutaneous nodules associated with SLE.

Irgang (1940) described that the involvement of subcutaneous adipose tissue by SLE would be the lupus erythematosus profundus. Some authors use the terms lupus panniculitis and lupus erythematosus profundus as synonyms, while others claim that the presence of skin changes overlying the lesion is called lupus erythematosus profundus (Morgan & Callen, 2001).

Arnold (1948) proposed the name lupus erythematosus profundus Kaposi-Irgang, called Irgang-Kaposi Syndrome by some authors (Guerre *et al.*, 2009; Mosier *et al.*, 2013; Sabaté *et al.*, 2006).

Lupus panniculitis is more frequent in the arms, shoulders, buttocks, thighs, and face, rarely reaching the breasts (Arsenovic & Terzic, 2008; Cerveira *et al.*, 2006). Tuffanelli (1971) identified the first case of lupus panniculitis in the breasts. Thus, when breast subcutaneous adipose tissue is involved in lupus panniculitis, it is called lupus mastitis (LM) (Summers *et al.*, 2009).

Winkelman (1983) cited the first case of LM in men. Although approximately 90% of the cases of LM affect women of childbearing age, men can also present it (Cerveira *et al.*, 2006).

Clinically and radiologically, LM presents as firm and painful breast subcutaneous nodules associated with overlying skin lesions (Summers *et al.*, 2009). Because these findings mimic malignant conditions, histopathological analysis is necessary to exclude malignancies and confirm LM since the disease has well-defined histological diagnostic criteria (Cerveira *et al.*, 2006; Summers *et al.*, 2009).

The surgical trauma can exacerbate the disease, therefore, opting for minimally invasive diagnostic procedures and conservative treatment is the best choice. LM is a benign pathology with a great response to drug therapy, being essential to carry out a correct and accurate diagnostic approach (Bayar *et al.*, 2007).

Due to the rarity of this type of lupus manifestation and, above all, in males, the present review aimed to analyze the pathophysiological aspects of the disease, epidemiology, clinical presentation, radiological and histopathological findings, differential diagnoses, and treatment. It is relevant to disseminate the LM before the academic community and draw the attention of this pathology as one of the differential diagnoses in the approach to breast lesions in men, especially in male breast cancer.

## 2. Methodology

The research and the literature review were carried out in the PubMed / Medline, Scopus, Scielo, Embase, Web of Science, and Google Scholar databases, known as gray literature. Studies related to lupus mastitis in men were selected through the combination of indexes present in the MeSH (Medical Subject Headings) Platform - PubMed / Medline: Mastitis, Lupus erythematosus panniculitis, Breast diseases, Male breast neoplasms, Male breast tumors, Men's health. Relevant scientifically validated studies carried out in humans in the cohort modalities, systematic review, reviews, case-control, cross-sectional, case series, case reports, and randomized clinical trials were included. The analysis and selection of the articles were carried out in pairs, blindly and separately, based on the reading of the title and abstract, with a third reviewer in case of disagreement. Studies that addressed other topics involving SLE, and did not have a full text or at least one keyword in the title or abstract, were excluded from the research (Pereira *et al.*, 2018).

## 3. Results and Discussion

### 3.1 Epidemiology

All ethnic groups, genders, and age groups are liable to develop lupus panniculitis and, consequently, LM. Lupus panniculitis occurs in about 2-3% of patients with lupus (Arsenovic & Terzic, 2008). Although most cases of LM occur in adult women, due to the higher prevalence of lupus in women of childbearing age, men can also be affected (Mosier *et al.*, 2013).

In the literature, there are around 50 published cases of LM, five of which in men (Kinonen *et al.*, 2010; Sharma *et al.*, 2020; Voizad *et al.*, 2017; Warne *et al.*, 2011). Therefore, a 9:1 ratio for women compared to men. Summers *et al.* (2009) also found this proportion.

Most male patients have a previous diagnosis of lupus, and one patient was diagnosed with LM being the first lupus manifestation (Kinonen *et al.*, 2010; Thapa *et al.*, 2016; Voizad *et al.*, 2017).

The average age of men at the time of the LM diagnosis is 43.5 years (39-50 years). Thus, there is a higher prevalence of the diagnosis in middle-aged adults. In cases of previously diagnosed lupus, the time of evolution until the onset of LM is approximately 13 years in male patients (Martella *et al.*, 2008). There is no description of these patients' ethnicity. Table 1 summarizes the epidemiological data of LM cases in men.

**Table 1.** Epidemiological data and clinical manifestations of published cases of LM in men.

Study	Gender/Age	Pathological history	Clinical manifestations
<b>Crevits (2009)</b>	Male, 50 years old	Controlled SLE (diagnosis time not specified).	Progressive and painful growth of the right breast for 6 months, hardened on palpation, without skin changes.
<b>Fernandez-Flores (2006)</b>	Male, 42 years old	Not specified.	Moderate and diffuse enlargement of the left breast, red and scaly plaque.
<b>Martella (2008)</b>	Male, 43 years old	SLE for 13 years and Antiphospholipid antibody syndrome.	Lump in the left breast for three months, irregular and solid, measuring 2 x 2 cm, no skin changes. Ipsilateral axillary lymph node enlargement measuring 1.5 cm.
<b>Thapa (2016)</b>	Male, 39 years old	No previous history of comorbidities. It was the first manifestation of the DLE.	Gradual increase of bilateral breast lumps for 18 months. Palpable subcutaneous mass, measuring 3 x 3 cm on the left and 2 x 2 cm on the right.
<b>Winkelmann (1983)</b>	Male, age not specified	Not specified.	Not specified.

Source: Authors (2021).

### 3.2 Etiology / Pathophysiology

SLE is a chronic autoimmune disease with a heterogeneous presentation that affects the organism through autoantibodies and immune complexes. When there is only skin involvement, it is called DLE. Lupus panniculitis is a rare manifestation of SLE or DLE in the subcutaneous tissue, and when it affects the breasts is called lupus mastitis (LM) (Summers *et al.*, 2009).

The evolution of LM can occur during or after the active course of SLE or be the first manifestation of lupus (Summers *et al.*, 2009). In the literature, there are rare reports of LM as the primary manifestation of SLE or DLE. In male patients, there is only one report, described by Thapa *et al.* (2016).

The exact pathophysiology of lupus mastitis is undefined (Kinonen *et al.*, 2010). According to Goulabchand *et al.* (2020), the immunomodulatory role of the mammary glands associates with the pathophysiology of autoimmune diseases. The principal evidence points to a relationship between LM and autoimmune activity, in which autoantibodies and immune complexes cause initial tissue damage in the breast (Summers *et al.*, 2009).

In this regard, researchers proved the presence of immunocomplexes in the areas affected by LM through direct immunofluorescence of blood vessels and the dermis-epidermis junction of the basement membrane (Cerveira *et al.*, 2006; Kinonen *et al.*, 2010; Summers *et al.*, 2009). Another point that confirms the autoimmune concept is that the indicated treatments are based on immunosuppression and obtain positive and scientifically validated results (Kinonen *et al.*, 2010; Summers *et al.*, 2009).

In patients with DLE, the involvement of the panniculus occurs from the propagation of the cutaneous inflammatory process, reaching subcutaneous and deep tissues (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002). In patients without a previous skin lesion, the deep inflammation of the panniculus adiposus results from lymphocytic vasculitis (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002).

In addition, it is possible to trigger or exacerbate the lesion after trauma, especially surgical trauma, such as performing a biopsy for LM histopathological confirmation (Cerveira *et al.*, 2006; Georgian-Smith *et al.*, 2002; Kinonen *et al.*, 2010).

Once the inflammatory process has started, the disease follows its evolutionary course through fat necrosis, calcification, fibrosis, scarring, and breast atrophy (Georgian-Smith *et al.*, 2002; Goulabchand *et al.*, 2020; Rosa & Mohammadi, 2013).

### 3.3 Clinical Manifestations

The clinical presentation of LM is usually through palpable, firm, mobile, painful subcutaneous breast nodules, which can be single or multiple, unilateral or bilateral (Arsenovic & Terzic, 2008; Crevits *et al.*, 2009; Fernandez-Flores *et al.*, 2006; Martella *et al.*, 2008; Rosa & Mohammadi, 2013; Summers *et al.*, 2009; Thapa *et al.*, 2016). Deep masses resulting from vasculitis may not be palpable (Mosier *et al.*, 2013).

Nipple retraction and cutaneous involvement overlying the nodular mammary lesion are usually present. Erythema, violet color, hyperkeratosis, poikiloderma, hypertrichosis, the appearance of orange peel, and atrophy of the epidermis are some variations found, especially in DLE (Crevits *et al.*, 2009; Fernandez-Flores *et al.*, 2006; Kinonen *et al.*, 2010; Lee *et al.*, 2019; Rosa & Mohammadi, 2013).

In acute cases, the lesion is painful, and the skin may be violet or erythematous. The presence of skin changes in LM increases the breast cancer similarity (Voizad *et al.*, 2017).

In male patients, the most common complaints are progressive and diffuse growth of the subcutaneous mammary nodule, pain, hardened consistency, associated with skin erythema, and time of evolution between 3-18 months, from the beginning of the symptoms to medical care (Crevits *et al.*, 2009; Fernandez-Flores *et al.*, 2006; Martella *et al.*, 2008; Thapa *et al.*, 2016). Table 1 summarizes the clinical manifestations data of LM cases in men.

Because it is a chronic disease, during its course alternates periods of remission and recurrence of the lesion, in the same initial site or even in the contralateral breast (Kinonen *et al.*, 2010; Mosier *et al.*, 2013). When spontaneously regressing, it is possible to cause lipoatrophy areas and atrophic scar or even not to leave sequelae (Arsenovic, & Terzic, 2008; Kinonen *et al.*, 2010; Mosier *et al.*, 2013; Sabaté *et al.*, 2006). In advanced cases and without the correct treatment, ulcerations, painful mass persistence, and skin retraction occur (Cho *et al.*, 2008; Summers *et al.*, 2009).

The association with lymph node enlargement, especially in the axillary region ipsilateral to the nodular lesion, can be found in some patients. In male patients, Martella *et al.* (2008) reported the presence of palpable ipsilateral axillary lymph node enlargement. Lymph node enlargements are reactive to the inflammatory process of LM, however, ruling out malignancy should only be done through histopathological analysis (Voizad *et al.*, 2017).

Systemic symptoms of panniculitis are not usual and, when present, are related to other forms of SLE. Approximately 50% of patients with panniculitis have mild types of systemic lupus (Summers *et al.*, 2009).

In the literature, although rare, there are reports of association of LM with other autoimmune diseases, such as polyarteritis nodosa (Vineetha *et al.*, 2016). In men, mastitis was associated with the antiphospholipid antibody syndrome (Martella *et al.*, 2008).

Among the serum tests, it is possible to observe the positivity of antinuclear antibodies, extractable nuclear antigens and anti-DNA antibodies, high erythrocyte sedimentation rate, and consumption of complement C4 (Guerre *et al.*, 2009; Summers *et al.*, 2009). The alteration in these exams has no diagnostic significance, and they are usually not measured (Summers *et al.*, 2009).

Thapa *et al.* (2016) showed, in a male patient, positive antinuclear antibody and negative anti-DNA antibody. On the other hand, Fernandez-Flores *et al.* (2006) reported a patient with LM and negative tests for antinuclear antibodies, extractable nuclear antigens, and anti-DNA antibodies. These findings corroborate the low sensitivity of serum diagnostic methods for LM.

Thus, the initial diagnostic hypothesis of LM should be clinical, and the doctor must be attentive to the signs and symptoms of the disease to identify it early.

### **3.4 Radiology**

In the clinical suspicion of LM, a radiological evaluation is mandatory. The most used and indicated imaging exams in a suspected breast lesion are mammography, ultrasound (US), and magnetic resonance imaging (MRI). It is interesting to associate more than one of the available methods to have more detailed analysis (Thapa *et al.*, 2016).

Below are shown the main features found in each radiological method. Table 2 exposes the imaging tests performed and the imaging findings described in the published male LM cases.

#### **3.4.1 Mammography**

The affected breast presents an increase of tissue densification, with a heterogeneous, irregular, and ill-defined mass (Thapa *et al.*, 2016). Initially, microcalcifications with thin and linear ramifications can exist, which gradually become more coarse to form the dystrophic calcifications characteristic of fat necrosis (Crevits *et al.*, 2009; Lee *et al.*, 2019; Mosier *et al.*, 2013; Summers *et al.*, 2009).

The initial density and calcification findings, especially with the fine linear features on mammography, mimics breast cancer (Mosier *et al.*, 2013).

#### **3.4.2 Breast ultrasound**

The ultrasound findings show a heterogeneous subcutaneous mass, with irregular and ill-defined margins, hypoechoic in its initial phase (fibrotic phase) (Lee *et al.*, 2019; Martella *et al.*, 2008; Mosier *et al.*, 2013). As the disease progresses, the lesion begins to have an acoustic shadow due to calcifications, and a hyperechoic focus, due to the infiltration of the subcutaneous cell tissue and the breast parenchyma (Mosier *et al.*, 2013; Thapa *et al.*, 2016; Voizad *et al.*, 2017).

Other modifications are the lesion extension to the subcutaneous fat, the skin thickening overlying the lesion, and intralesional vascularization (Lee *et al.*, 2019; Mosier *et al.*, 2013; Summers *et al.*, 2009; Thapa *et al.*, 2016). The cutaneous alteration seen in the image must be carefully analyzed, as it may represent an advanced carcinoma manifestation (Cho *et al.*, 2008; Sabaté *et al.*, 2006).

In a male patient with bilateral breast lesions, Thapa *et al.* (2016) identified the presence of multiple small bilateral axillary and cervical lymph nodes with attenuation of the hilum on ultrasound examination.

#### **3.4.3 Magnetic Resonance Imaging**

There are few reports of its application in LM. Despite being convenient in assessing the extent of the lesion, cutaneous involvement (thickening), and response to treatment, it has low specificity in the differential diagnosis with malignancy (Cho *et al.*, 2008; Mosier *et al.*, 2013; Sabaté *et al.*, 2006; Summers *et al.*, 2009).

The T1 sequence shows an irregular, heterogeneous mass, with thick peripheral enhancement and an aspect of fat necrosis (Lee *et al.*, 2019; Mosier *et al.*, 2013; Sabaté *et al.*, 2006; Summers *et al.*, 2009; Thapa *et al.*, 2016). At T2, the lesion shows signs of peripheral hypointensity and central hyperintensity (Sabaté *et al.*, 2006; Thapa *et al.*, 2016).

Thapa *et al.* (2016) were the first to report the use of MRI in a male patient. Enhancement kinetics demonstrated a type 1 pattern, a feature of a benign lesion.

Computed tomography (CT) is not usually used in breast evaluation. Only Martella *et al.* (2008) used CT in men and found hypertrophy of the axillary lymph nodes.

**Table 2.** Imaging exams and radiological findings of published cases of LM in men.

Study	Imaging Exams and Radiological findings
<b>Crevits (2009)</b>	Mammography: diffuse coarse pleomorphic calcifications in the right breast, similar to fat necrosis calcifications
<b>Fernandez-Flores (2006)</b>	Not specified.
<b>Martella (2008)</b>	Breast ultrasound: echogenic subcutaneous nodule with irregular margins, measuring 36 mm CT: hypertrophy of the axillary lymph nodes on the left
<b>Thapa (2016)</b>	Mammography: dense ill defined mass, asymmetrical in both breasts. Absence of calcifications, distortion of architecture and skin retraction. BI-RADS 4 <sup>a</sup> Left breast ultrasound: subcutaneous hyperechoic mass, ill defined, with internal vascularity, measuring 25x7mm Right breast ultrasound: subcutaneous mass, hyperechoic, ill defined, measuring 22 x 9 mm Axilla ultrasound: multiple lymph nodes <1 cm, bilateral, with attenuated hilum MRI: focal areas of fat with overlying skin thickening, hyperintense in T2. In contrast, the lesions showed heterogeneous enhancement predominantly in T1
<b>Winkelmann (1983)</b>	Mammography: ductal calcifications.

Source: Authors (2021).

### 3.5 Biopsy / Histopathological

Because the association between clinical and radiological examinations is often inconclusive for LM and due to the high similarity to breast cancer, the biopsy assists in the correct diagnosis and avoids surgery in a disease with clinical treatment (Thapa *et al.*, 2016). Table 3 shows the biopsy methods and the histopathological findings of published cases of LM in men.

The accomplishment of invasive procedures in the lupus lesion can exacerbate the disease and make healing difficult or provide a painful and chronic ulcer. In this sense, biopsies should perform through minimally invasive procedures (Mosier *et al.*, 2013; Rosa & Mohammadi, 2013; Summers *et al.*, 2009). Currently, the recommended method is the core needle biopsy, as it is less invasive, allows lesser local trauma, and provides good diagnostic results (Lee *et al.*, 2019; Lucivero *et al.*, 2011; Sabaté *et al.*, 2006; Thapa *et al.*, 2016).

Thapa *et al.* (2016) performed the core needle biopsy in male patients and did not report exacerbation or worsening of the inflammatory condition. Martella *et al.* (2008) performed fine-needle aspiration biopsy (FNAB), another minimally invasive method, but obtained inconclusive results, having to opt for an open excisional biopsy. Although there was no worsening, studies show the potential risk of this surgical action (Kinonen *et al.*, 2010; Lucivero *et al.*, 2011). Therefore, it is necessary to institute an adequate diagnostic strategy to avoid multiple biopsies.

Due to the possibility of post-procedure LM exacerbation, some authors suggest that the biopsy should be performed only after therapeutic failure of the conservative empirical treatment (Voizard *et al.*, 2017).

Crevits *et al.* (2009) did not perform a biopsy and diagnosed LM in a male patient based on the clinical features and imaging exams. However, under the hypothesis of malignancy, the fact of exacerbating the lesion should not prevent biopsy for diagnostic confirmation.

The most common histopathological findings of LM are lymphocytic panniculitis and hyaline fat necrosis (Kinonen *et al.*, 2010). Lymphocytic panniculitis characterizes by infiltration of small mature lymphocytes associated with plasma cells (lymphoplasmacytic infiltrate), involving the fat lobule, periseptal, perilobular, and periductal areas (Kinonen *et al.*, 2010; Rosa & Mohammadi, 2013; Summers *et al.*, 2009). Hyaline fat necrosis determines by anucleated adipocytes in a glassy collagenous stroma fund (Kinonen *et al.*, 2010; Mosier *et al.*, 2013).

Lymphocytic vasculitis infiltrating small and medium caliber vessels may be present. Microcalcifications appear in advanced cases. Other findings are sclerosis, lobular and ductal atrophy, fibrosis, germinal centers, lymphoid follicles, mucin deposit, hyalinization of the subdermal papillary zones, and skin changes of the DLE (Kinonen *et al.*, 2010; Rosa & Mohammadi, 2013; Summers *et al.*, 2009).

There is a predominance in LM male patients of lymphocytic panniculitis and vasculitis, with lobular and septal lymphocytic infiltrate. Other changes found were hyaline fat necrosis, perivascular inflammation, presence of lymphoid follicles, vacuolar changes in the dermo-epidermal junction, and thickening of the basement membrane (Fernandez-Flores *et al.*, 2006; Martella *et al.*, 2008; Thapa *et al.*, 2016).

Histopathological findings of LM are divided into major and minor criteria. Major criteria are hyaline fat necrosis, lymphocytic infiltrate with lymphoid nodules involving necrosis, lobular or periseptal panniculitis, and microcalcifications. Minor criteria are lymphocytic vasculitis, mucin deposition, hyalinization of the subdermal papillary zones, and discoid lupus erythematosus alterations on the overlying skin (Cerveira *et al.*, 2006).

In addition to collaborating in the differential diagnosis, the criteria are considered virtually pathognomonic for LM, and it is not necessary to have all the features to confirm the diagnosis (Cerveira *et al.*, 2006; Voizad *et al.*, 2017; Warne *et al.*, 2011).

Thus, even in patients without a previous diagnosis of SLE or DLE, the findings strongly suggest the involvement of lupus panniculitis, with the doctor being responsible for the clinical and laboratory investigation of lupus and the follow-up of these patients.

The association between necrosis, sclerosis of the dermis collagen, and lymphocytic infiltrate is responsible for the hardened consistency of the lesion on clinical examination and increased breast densification in radiology (Nigar *et al.*, 2007).

In the analysis by direct immunofluorescence, the LM findings show linear deposition of the IgM immunoglobulin and the C3 complement at the dermo-epidermal junction and around the blood vessels (Cernea *et al.*, 1993; Cerveira *et al.*, 2006).

Immunohistochemistry represents a significant aid in the differential diagnosis, especially in the differentiation of lymphoproliferative and oncological diseases from benign pathologies. The results reveal, in general, a combination of CD20+ B lymphocytes and CD3+ and CD4+ T lymphocytes (Kinonen *et al.*, 2010).

Fernández-Flores *et al.* (2006) analyzed immunohistochemistry in cases of LM in men and demonstrated the presence of type B (CD20+) and T (CD3+, CD4+, CD8-) lymphocytes and histiocytes (CD68+). In addition, they performed the analysis of a molecular study based on the polymerase chain reaction (PCR), showing polyclonal rearrangement of IgH (CDR2 and CDR3) and T-cell gamma-receptor (Fernandez-Flores *et al.*, 2006).



**Table 3.** Biopsy and histopathological findings of published cases of LM in men.

Study	Histopathological / Immunohistochemistry
<b>Crebits (2009)</b>	Not performed.
<b>Fernandez-Flores (2006)</b>	Mixed septal and lobular lymphocytic panniculitis, lymphoid follicular infiltrate, lymphocytic vasculitis, vacuolar changes at the dermo-epidermal junction, and thickening of the basement membrane Immunohistochemistry showed B (CD20+) and T (CD3+, CD4+, CD8-) lymphocytes, and histiocytes (CD68+). PCR demonstrated polyclonal rearrangement of IgH (CDR2 and CDR3) and T-cell gamma-receptor
<b>Martella (2008)</b>	FNAB: C2 (benign findings according to the 1997 European guideline) Open excisional biopsy: panniculitis with areas of hyaline necrosis, perivascular inflammation, and vasculitis
<b>Thapa (2016)</b>	Ultrasound-guided core biopsy: fibrofatty tissue infiltrated by lymphoplasmacytic cells with a lobular and septal distribution. Some vessels had sclerosis, edema, and lymphocytic infiltration
<b>Winkelmann (1983)</b>	Not specified.

Source: Authors (2021).

### 3.6 Differential diagnosis

For being a rare pathology, LM is often not remembered, making its diagnosis difficult. Despite the clinical evaluation associated with imaging and histopathological exams confirming the diagnosis, during its evolution phases, LM mimics malignant diseases. Thus, performing the differential diagnosis is essential.

The hypothesis of breast cancer should always be considered. Among the histological types, inflammatory and medullary breast carcinomas are the most similar to LM (Rosa & Mohammadi, 2013; Warne *et al.*, 2011).

In the early stages, LM appears as a solitary nodule, hardened and associated with skin changes, making it even more similar clinically and radiologically to cancer (Arsenovic & Terzic, 2008; Crebits *et al.*, 2009; Martella *et al.*, 2008; Thapa *et al.*, 2016). Imaging exams do not contribute much to differentiation and, therefore, histology should rule out the presence of malignant cells (Rosa & Mohammadi, 2013; Warne *et al.*, 2011).

When LM cutaneous alterations are present, such as redness and the “orange peel” aspect, the lesion simulates inflammatory breast carcinoma (Cernea *et al.*, 1993; Rosa & Mohammadi, 2013). In imaging, both manifest as masses, densification, and microcalcifications (Voizad *et al.*, 2017). MRI can be helpful to indicate, through post-contrast enhancement, the best site for biopsy in the malignancy suspicion (Voizad *et al.*, 2017). Histopathological analysis reveals infiltration of tumor cells in the lymphatic vessels of the dermis (Rosa & Mohammadi, 2013).

The differential diagnosis with medullary carcinoma becomes most significant when the pathologist receives insufficient samples of the lesion and describes a predominance of peripheral lymphoplasmacytic reaction (Rosa & Mohammadi, 2013). This failure occurs due to an error in the biopsy technique, reaching only the tumor periphery and not obtaining cancer cells (Kinonen *et al.*, 2010; Rosa & Mohammadi, 2013). Immunohistochemistry is indicated to assist, above all, the use of cytokeratin staining (Kinonen *et al.*, 2010). In the absence of malignant cells, the radiological and macroscopic characteristics in

the anatomopathological can help since the lesions of the medullary carcinoma are usually larger and delimited (Kinonen *et al.*, 2010; Warne *et al.*, 2011).

Breast lymphoma is usually metastatic non-Hodgkin lymphoma. On physical examination, it may manifest as a breast lump and be associated with ipsilateral axillary or generalized adenopathy (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002). Mammography usually shows single or multiple dense nodules, unilateral or bilateral. Calcifications and skin ulceration are not common (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002; Mosier *et al.*, 2013). In histopathology, the presence of perivascular lymphocytic infiltration in breast tissues should increase the degree of the disease, while the presence of germinal centers contributes to the exclusion (Mosier *et al.*, 2013; Summers *et al.*, 2009; Georgian-Smith *et al.*, 2020). Immunohistochemical analysis is of great value in differential diagnosis (Mosier *et al.*, 2013).

Although rare, a specific histological type of non-Hodgkin lymphoma, subcutaneous panniculitis-type T-cell lymphoma, can appear in the breast (Kinonen *et al.*, 2010; Rosa & Mohammadi, 2013). Clinically similar to LM, it presents recurrent subcutaneous nodules associated with erythematous plaques (Rosa & Mohammadi, 2013). Histopathological examination shows a lobular lymphocytic infiltrate, simulating lobular panniculitis (Rosa & Mohammadi, 2013). Such lymphocytes appear to be atypical and larger than those found in LM, although there is a predominance of small and medium lymphocytes in the histological visualization (Kinonen *et al.*, 2010).

Another difference for LM is the typical presence of coagulative fat necrosis and the absence of germinal centers (Kinonen *et al.*, 2010; Mosier *et al.*, 2013). Immunohistochemistry and T-cell receptor gene rearrangement collaborate to investigate and exclude the clonality of T-cells, which is present in lymphoma (Kinonen *et al.*, 2010).

Granulomatous mastitis is a rare affection of the breasts, usually normal on mammography and clinically very similar to LM because it manifests remissions and exacerbations (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002). In histological examination, it presents a granulomatous reaction formed by lymphocytes, histiocytes, plasma cells, and, rarely, eosinophils, which may be associated with the erasure of the lobular architecture and the formation of microabscesses (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002). The cytological exam also shows to be helpful in the differential diagnosis with LM (Yip *et al.*, 2000).

The diabetic mastopathy, as it evolves as a firm and painful palpable mass, is part of the differential diagnoses of LM, even though radiologically and laboratory tests can be ruled out, especially in patients known to be diabetic (Mosier *et al.*, 2010; Rosa & Mohammadi, 2013).

In histology, diabetic mastopathy presents lymphocytic infiltrate restricted to small groups of perilobular, periductal and perivascular lymphocytes, dense “keloid-like” fibrosis, and growth of stromal cellularity with myofibroblasts (Goulabchand *et al.*, 2020; Kinonen *et al.*, 2010; Rosa & Mohammadi, 2013). In contrast, the lymphocytic infiltrate of the LM is less restricted and has a predominantly lobular disposition (Kinonen *et al.*, 2010; Rosa & Mohammadi, 2013; Warne *et al.*, 2011).

Breast tuberculosis, depending on the endemic region of the disease, is also a differential diagnosis (Wani *et al.*, 2009). The association with laboratory and imaging tests is significant to assess the extra-mammary involvement by *Mycobacterium tuberculosis*. Histopathological examination reveals caseous necrosis and epithelioid cell granulomas (Mosier *et al.*, 2013).

Granulomatous mastitis, diabetic mastopathy, and mammary tuberculosis have some characteristics in common. In these lesions, the masses do not show MRI enhancement, unlike LM, which presents post-contrast peripheral enhancement (Mosier *et al.*, 2013). The marked histopathological difference of granulomatous diseases and diabetic mastopathy for LM is the absence of lymphocytic vasculitis and hyaline fat necrosis (Arsenovic & Terzic, 2008; Georgian-Smith *et al.*, 2002; Mosier *et al.*, 2013; Rosa & Mohammadi, 2013).

A localized form of scleroderma, morphea, in its stage of lipoatrophy also characterizes a differential diagnosis of LM. The cutaneous lesions are shown as hardened plaques, ranging from hypochromic coloring to erythematous, in cases of active

disease (Cernea *et al.*, 1993; Voizard *et al.*, 2013). Histopathological evaluation reveals lymphocytic vasculitis, atrophy of the epidermis, and tissue replacement by collagen fibers (Cernea *et al.*, 1993; Kinonen *et al.*, 2010). Differentiation is evident on direct immunofluorescence, where LM demonstrates deposition of IgG, IgM, and C3 in the basement membrane of the epidermis, while morphea does not show such changes (Cernea *et al.*, 1993).

### **3.7 Treatment / Follow-up**

After the diagnosis, the initial treatment should be clinical. The use of hydroxychloroquine, an antimalarial, is considered the first therapeutic option (Cerveira *et al.*, 2006; Dandinoglu *et al.*, 2013; Voizard *et al.*, 2017). The recommended dose for LM treatment is 200mg/day (Summers *et al.*, 2009). In men, there is a good response of LM after the institution of the antimalarial therapy, and remission is expected 3 to 6 months after the beginning of clinical treatment (Cernea *et al.*, 1993; Summers *et al.*, 2009; Thapa *et al.*, 2016). Table 4 summarizes the treatment and follow-up used in published cases of LM in men.

The combination with systemic corticosteroids is indicated in cases without response to antimalarials and may use prednisone at a dose of 1mg/kg/day (Summers *et al.*, 2009). Thapa *et al.* (2016) associated hydroxychloroquine and prednisolone, obtaining good results in a male patient. The application of topical corticosteroids is not effective in controlling the disease (Summers *et al.*, 2009; Voizard *et al.*, 2017).

For lesions unresponsive to the initial management and to avoid chronic corticosteroids use, immunosuppressants such as cyclophosphamide and intralesional triamcinolone acetonide may be applied (Castro *et al.*, 2004; Cernea *et al.*, 1993; Mosier *et al.*, 2013).

Other corticosteroid-sparing immunosuppressive drugs used in the treatment of lupus and amenable to application in LM are methotrexate and azathioprine, although their use in LM in men has not yet been reported (Yan *et al.*, 2020). Some studies mention the possibility of using dapsone and thalidomide, especially if there are adverse reactions to hydroxychloroquine (Fernandez-Torres *et al.*, 2009; Rosa & Mohammadi, 2013).

Surgical treatment through mastectomy should be avoided since surgical trauma can favor the progression and the disease worsening. Surgical procedures are reserved only for cases clinically refractory to drug therapies and in situations where there is a high suspicion of malignancy (Bayar *et al.*, 2007; Castro *et al.*, 2004; Cerveira *et al.*, 2006; Dandinoglu *et al.*, 2013; Summers *et al.*, 2009).

The follow-up of the patient is necessary to monitor the evolution of the condition and possible recurrences. MRI plays a relevant role in the LM patient's follow-up. As treatment starts, the peripheral enhancement of the lesion becomes more tenuous and discontinuous (Lee *et al.*, 2019; Mosier *et al.*, 2013). Thapa *et al.* (2016) reported an expressive improvement in the symptoms and the ultrasound aspect of the breast in 45 days after the treatment institution.

**Table 4.** Treatment and follow-up of published cases of LM in men.

Study	Treatment / Follow-up
<b>Crebits (2009)</b>	Not specified.
<b>Fernandez-Flores (2006)</b>	Not specified.
<b>Martella (2008)</b>	Not specified.
<b>Thapa (2016)</b>	Hydroxychloroquine and Prednisolone Significant reduction of the swelling and pain after 45 days of treatment. Ultrasound showed a decrease in the size of the lesion.
<b>Winkelmann (1983)</b>	Antimalarial drugs

Source: Authors (2021).

#### 4. Conclusion

LM is a rare form of lupus erythematosus profundus that affects patients with SLE or DLE and maybe the first manifestation of the disease. Clinically it appears like a breast mass associated with local inflammatory signs, and the differential diagnosis with breast cancer is necessary and challenging.

The clinical-radiological correlations are significant to direct the investigation and suggest a biopsy through minimally invasive procedures to avoid exacerbation and worsening of the lesion. The presence of lymphocytic infiltration and hyaline fat necrosis in the histopathology, associated with the clinical history, permits the pathologist to diagnose the LM.

Prior knowledge of the condition allows the development of a hypothesis, the correct diagnostic investigation, and, consequently, early treatment, avoiding the worsening of the disease. The treatment of choice should be antimalarials and associated with corticosteroids if refractory or recurrent disease.

Although breasts are more related to women, socially, emotionally, physiologically, and anatomically, men can also suffer from breast disorders. Care is essential, and it is up to the physician to perceive LM in the early stages and provide an appropriate therapeutic approach.

For the future, randomized trials and systematic reviews with meta-analysis are of great value to guide a better approach to the patient with lupus mastitis, aiming at an early and correct diagnosis and adequate disease control with fewer exacerbations, complications, and sequelae.

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