Diabetic mastopathy: spectrum of radiological findings.

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Learning objectives

The main objective of this revision is to illustrate the spectrum of radiological manifestations of diabetic mastopathy in the different breast imaging techniques: mammography, ultrasound and magnetic resonance (MRI).

To help in this objective, a brief review of the literature has also been done, emphasizing the clinical and pathological aspects and the current recommended management of this rare disease.
Background

Diabetic mastopathy is a rare benign complication of the breast due to long-standing Diabetes Mellitus that was first described by Soler and Khardori in 1984, and consists of an increase in consistency of the glandular tissue.

The increase of consistence and density is secondary to fibrous proliferation whose clinical manifestation is as a well-defined painless palpable hard breast lump or mass that is clinical and radiologically indistinguishable from breast cancer, although frequently is multi-centric or involves both breasts. Pathologically this entity present focal areas of fibrosis which show B cell-predominant lymphocytic lobulitis, ductitis, and vasculitis.

Typically occurs in young premenopausal women between 20 - 50 years old with a long-standing history of insulin dependent Diabetes Mellitus (Type 1) greater than 15 years, often with other multiple microvascular complications associated, mainly retinopathy, but also neuropathy and, nephropathy. It accounts for less than 1% of benign breast lesions but despite it´s rarity, it has been found in up to 13% of insulin-dependent pre-menopausal patients.

It has also been described in diabetic patients who are non-insulin dependent, as well as in patients with other endocrine diseases, particularly of the thyroid, and in men.

Breast lesions caused by diabetic mastopathy often clinical and radiologically mimics a breast carcinoma, so the differentiation from cancer sometimes may be difficult and a biopsy could be required. There is no increased risk of breast cancer in these patients.

Although there are several hypothesis, the cause of this "fibrous reaction" remains unknown.
Findings and procedure details

PATHOGENESIS

Although the pathogenesis of diabetic mastopathy remains unknown, several mechanisms have been suggested.

The most widely accepted theory relates to the production of non-enzymatically glycosylated proteins (advanced glycosylation end products) that are often cross-linked and resistant to degradation, and deposited within the matrix of the breast. The end products create a "neo-antigen" that triggers secondary autoimmune response with B cell proliferation and antibody formation. This manifests as a localized autoimmune reaction and results in cytokine release, perivascular proliferation of B-lymphocytes and inflammation of lobular epithelium, as well as further matrix expansion proliferation of collagen and epithelioid fibroblasts. This pattern of inflammation is similar to that seen in autoimmune disorders of other tissues, such as Sjögren's syndrome and Hashimoto's thyroiditis. However, the proliferation of B-cells is not clonal, and therefore is not thought to pose any increased risk for lymphoma.

Other authors have suggested that exogenous insulin might lead to the development of diabetic mastopathy through an inflammatory or immunologic reaction to insulin, the vehicle, or a contaminant in the vehicle, but this hypothesis does not justify cases in non-insulin dependent Diabetes Mellitus.

Recently, another theory has suggested a link between amyloidosis and diabetic mastopathy, proposing that the amyloid may be related to the immunoglobulin produced by plasma cells in the inflammatory infiltrate.

Although many mechanisms have been offered about the cause of diabetic mastopathy, none has been proven.

CLINICAL MANIFESTATIONS

Clinically diabetic mastopathy presents in the physical examination as a diffuse nodularity or painless masses of stony consistency that may be uni or bilateral, unique or multiple.
Commonly are multiple, multi-centric or bilateral (60% of the cases), and are predominantly located in the subareolar region. Some of them can be painful, however the majority are not.

A wide range of terms have been used to describe them: well-defined, discrete, rock hard, firm, irregular.

The findings of the physical examination are indistinguishable from those of breast cancer, simulating those of scirrhous or invasive lobular breast cancer.

**DIAGNOSIS**

**MAMMOGRAPHY**

Mammography is usually the first imaging technique employed in the assessment of these patients. Diabetic mastopathy normally shows an extraordinary density, frequently bilateral. In these cases, another imaging procedure is always needed.

The most common mammographic findings are regional asymmetric increased opacity with ill-defined margins corresponding to the site of the presenting breast mass and with no associated calcifications, spiculations, overlying skin change or axillary lymphadenopathy (Fig. 1 on page 12, Fig. 2 on page 12).

In other cases, lesions are often masked by dense glandular tissue, making mammographic evaluation difficult. In this patients it is impossible to identify nodules or masses because of the extraordinary density of all the glandular tissue (Fig. 3 on page 13).

There are no specific features conclusive enough to make a diagnosis of diabetic mastopathy and to exclude malignancy on mammogram alone.

**ULTRASOUND**

Ultrasound often reveals the most characteristic imaging findings of the disease: poorly demarcated and ill-defined irregular hypoechoic masses of between 2 - 6 cm, with moderate to marked posterior acoustic shadowing (Fig. 4 on page 14, Fig. 5 on page 15).
This marked shadowing correlates with the amount of fibrous tissue and a more advanced stage of disease, and is more prominent than that seen in breast cancer, although these findings are indistinguishable from malignancy (Fig. 6 on page 16).

Colour flow ultrasound show no Doppler signal. An absence of Colour Doppler signals in an indeterminate breast mass is more frequently associated with a benign lesion because breast cancer increase vascularity on colour Doppler ultrasound (Fig. 7 on page 16).

Ultrasound is also useful for guided core biopsy and for monitoring the disease following diagnosis (Fig. 8 on page 17).

It seems evident that ultrasound elastography, due to its ability to quantify tissue densities, can play an important role in this pathology. To our knowledge, nothing have been reported to date about the role that this technique can develop in diabetic mastopathy.

**MRI**

Dynamic MRI has also an important role in this pathology. It has been recently used to characterize these lesions when there is a high suspicion of malignancy in the previous tests or when diabetic mastopathy can confound the detection of breast carcinoma. The value of breast MRI also lies in its ability to detect possible malignant lesions in highly dense breast tissue.

Imaging findings are variable, ranging from decreased diffuse contrast material enhancement to rapid, intense enhancement that is indistinguishable from breast carcinoma.

Three contrast uptake patterns have been described:

- nonspecific patchy or diffuse stromal enhancement with no focal enhancing mass or rim (Fig. 9 on page 18).

- poor early phase enhancement which increased gradually and heterogeneous spotty enhancement in the delayed phase. Although scirrhous cancer may show similar findings, heterogeneous spotty enhancement may be one of the typical findings of diabetic mastopathy on MR images.
- homogeneously low enhancement with a gradual and progressive course and subsequent washout, a typical time intensity curve for a benign lesion (Fig. 10 on page 19).

It is important to emphasize that contrast enhancement will be slightly more prominent in the symptomatic breast than in the asymptomatic breast.

MRI enhancement kinetics and postprocessing image subtraction techniques helped to differentiate the benign diabetic mastopathy and breast cancer and to depict the wide extent of disease in this patient, thus aiding in staging the cancer (Fig. 11 on page 20).

Consequently, dynamic contrast enhanced MRI can help to differentiate diabetic mastopathy from malignancy but may not always be useful for differentiating diabetic mastopathy from breast cancer, which can show similar findings. Biopsy or surgical excision may be unavoidable in these cases.

CT

Heterogeneous spotty enhancement can be appreciated, but there is no evidence to suggest that CT may be useful in the diagnostic process of diabetic mastopathy.

PATHOLOGICAL CHARACTERISTICS

The diagnosis of diabetic mastopathy can only be made histopathologically, when there is also a history of diabetes.

Pathologically this entity corresponds to a lymphocytic mastitis. Morphologically is undistinguishable from other lymphocytic mastopathies associated to autoimmune diseases, although diabetic mastopathy include dense stromal fibrosis and lymphocytic infiltrates in association with ducts and lobules.

The histologic constellation of diabetic mastopathy is:

(a) Lymphocytic lobulitis and ductitis with glandular atrophy (Fig. 12 on page 21, Fig. 13 on page 22).

(b) Lymphocytic - mononuclear perivascular inflammation-predominantly B-cell
(c) Dense often keloid-like fibrosis (**Fig. 14 on page 23**, **Fig. 15 on page 24**, **Fig. 16 on page 25**).

(d) Epithelioid-like fibroblasts (**Fig. 17 on page 26**).

The most important findings are perilobar and perivascular lymphocytic infiltrate of mature B cells accompanied by intense keloidal fibrosis of the stroma with lobular atrophy and characteristic myofibroblastic epithelioid cells. This cells are rounded epithelioid cells with abundant cytoplasm and oval vesicular nuclei, which are individually isolated by collagen and distributed similarly to spindle fibroblasts. It was stated that they appear uniquely in diabetic mastopathy and are diagnostic when found, although they are not present in all cases and are not unique to patients with insulin-dependent diabetes mellitus.

Despite all these pathologic changes appear to be relatively specific for insulin-dependent diabetes mellitus, may also be seen in nondiabetic patients and in association with autoimmune disease in the absence of diabetes.

The presence in the adequate context of lymphocytic (primarily B cells) ductitis and lobulitis with varying degrees of keloidal fibrosis, vasculitis and epithelioid fibroblasts are diagnostic.

This figure resumes the main aspects to consider in order to establish the diagnosis of diabetic mastopathy.

**Fig. 18**

<table>
<thead>
<tr>
<th>Diagnosis of diabetic mastopathy</th>
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<tr>
<td>Painless, premenopausal women with long-standing type 1 diabetes mellitus that is usually associated with microvascular complications. The patient may or may not have a history of other endocrine or autoimmune diseases.</td>
</tr>
<tr>
<td>A palpable breast mass is identified on physical examination that is hard, nontender, and clinically suspicious for carcinoma.</td>
</tr>
<tr>
<td>Mammographic studies show an increased density but do not confirm the presence of a localized mass. Ultrasound also fails to identify a solid or cystic mass.</td>
</tr>
<tr>
<td>Excisional or core biopsy shows dense keloidal fibrosis associated with a perivascular, periductal, or perilobular lymphocytic infiltrate. Epithelioid fibroblasts may or may not be present.</td>
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References: Servicio de Radiodiagnostico, Hospital Universitario La Fe - Valencia/ES
MANAGEMENT

Clinical examination of the breast in long-standing insulin-dependent Diabetes Mellitus young women must be incorporated in their routine assessment.

Diagnosis

In a long-standing type 1 diabetic patient presenting with a firm or rock-hard, palpable breast mass, mammography and ultrasound must be the initial step in the diagnostic process although these techniques do not allow a specific diagnosis of diabetic mastopathy with confident exclusion of malignancy.

If the radiological findings are those typical of diabetic mastopathy, ultrasound-guided core biopsy must be performed in order to confirm histopathologically this suspicion.

When there is high suspicion of malignancy (clinical examination or radiological findings are not concordant with the normal features of diabetic mastopathy), we have already seen that MR can help in differentiating benign diabetic mastopathy from malignant breast cancer.

Core biopsy with a 14-gauge needle: Current practice would dictate that a core biopsy be performed for definitive diagnosis. Although surgical excision was usually performed to exclude malignancy, ultrasound-guided core biopsy is currently accepted as adequate for the diagnosis of this entity. Is a reliable method for establishing the diagnosis in the proper clinical setting and can eliminate the need for more aggressive procedures. Therefore, core needle biopsy under ultrasound guidance eliminates redundant surgical procedures that may exacerbate the condition.

Fine needle aspiration: Cytologic analysis does not often help in the diagnosis of diabetic mastopathy because approximately 50% of the aspirations obtained have "insufficient cellular material for evaluation". It can be used for serial monitoring of the condition but is not adequate as a diagnostic tool.

Despite previous data, fine needle aspiration can play a relevant role in the diagnostic process of diabetic mastopathy. The firm resistance experienced during the back-and-forth motion of the needle are stronger than that of other benign and malignant breast conditions, hence this could be a clue to the diagnosis of diabetic mastopathy.
**Surgical biopsy:** If the core biopsy is nondiagnostic, an open biopsy is indicated but if the core biopsy is diagnostic for diabetic mastopathy, no further intervention is required. Excision biopsy is only recommended if additional clinical or radiological features suspicious of malignancy or for cosmetic reasons.

Approximately 60% of the patients that underwent a surgical excision, recur after this. Recurrence tends to be in the same location and involves more breast tissue than the preceding lesion, therefore surgical biopsy should not be considered as a routine procedure in the diagnosis of diabetic mastopathy.

**Follow-up**

Once this benign condition is diagnosed, it should be managed as such. Patients should be advised about the condition and how to self examine the breasts. They should know that if there are any changes in size and number of breast lumps that they should consult the breast team.

In a patient with a prior diagnosis of diabetic mastopathy, a new lesion might be assessed by fine needle aspiration. If the cytologic and clinical findings are consistent with diabetic mastopathy, conservative clinical management could be considered. Although there is only a 50% of diagnostic success rate, ductal epithelial cells in clusters, lymphocytes and epithelioid fibroblasts can be identified. Depending on the adequacy of the sample, a core needle biopsy might then be indicated to rule out malignancy.

If the lesions become clinically or radiologically suspicious, more specific techniques are mandatory. In these circumstances, MRI and core biopsy should be determinant in order to rule-out malignancy.

**PROGNOSIS**

It has been reported that 60% of these lesions have single or multiple recurrence in the same or the contralateral breast in the first 5 years after surgical excision, but this recurrence tends to be in the same location, involving more breast tissue than the preceding lesion; therefore, surgical biopsy should not be considered because may exacerbate this condition.

Although there is a clonal lymphocytic proliferation, patients with diabetic mastopathy are not at an increased risk for developing breast cancer or breast lymphoma. Despite this fact, diagnosis and follow-up in these patients should be more careful because of the
possibility of confusing new onset cancer in a patient with diabetic mastopathy. Cancer can occur in these patients with the same prevalence than in general population, but, as we have previously seen, is more difficult to diagnose.
Fig. 1: The most common mammographic finding of diabetic mastopathy is a regional asymmetry. In this cranial-caudal (CC) projection an asymmetry in the subareolar region of left breast can be observed. This location is the most frequent of diabetic mastopathy.

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**Fig. 2:** Medio-lateral oblique (MLO) projection from same patient as figure 1.

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**Fig. 3:** It is not rare bilateral presentation in diabetic mastopathy. Both breasts show a quite homogeneous elevated density, being impossible to identify nodules. There is not associated calcifications, spiculations, or skin thickening.

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**Fig. 4:** Typical ultrasonographic findings in diabetic mastopathy: ill-defined, hypoechoic lesion with posterior acoustic shadowing.

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**Fig. 5:** The same as in mammography, ultrasound can evidence the typical findings of diabetic mastopathy in both breasts when there is a bilateral involvement.
**Fig. 6:** Sometimes, there is not posterior acoustic shadowing. The highest degree of this feature has been related to a more severe fibrosis in advanced stages.

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Fig. 7: Diabetic mastopathy doesn’t show Doppler signal because of the predominance of fibrous tissue.

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Fig. 8: Ultrasound-guided core biopsy. The 14G core biopsy needle can be seen as an echogenic line approaching the lesion.

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Fig. 9: MRI of a patient with bilateral involvement. A) T2-weighted sequence. B) Nonspecific patchy stromal enhancement after contrast administration. C and D) The two ROIs evaluated in both breasts show a benign behaviour.

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Fig. 10: MRI of a confirmed histopathologically diabetic mastopathy. A) Both breasts show a marked hypointensity in this T2-weighted sequence because of fibrosis. B) In the right breast, there is a nodule presenting a weak enhancement after contrast administration, C and D) The graphic shows the typical time intensity curve for a benign lesion.

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Fig. 11: In this patient there is a nodule in the right breast (A) with real enhancement confirmed in the sustraction post-process (B). This nodule also has a benign morphology in its time intensity curve (C and D).

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**Fig. 12:** Lymphocitic proliferation surrounding ducts and vessels (ductitis and vasculitis) surrounded by a dense stromal fibrosis (Hematoxylin and eosin stain (H&E), x10).

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Fig. 13: Dense infiltrate of small, mature lymphocytes affecting a lobular unit (H&E, x40).

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Fig. 14: Lobular sclerosis (H&E, x10).

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Fig. 15: Lobular sclerosis (H&E, x40).

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**Fig. 16:** Focus of dense keloidal fibrosis (H&E, x40).

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Fig. 17: Epithelioid cells with abundant eosinophilic cytoplasm and vesicular nuclei set within a fibrous stroma (H&E, x40).

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Conclusion

Although is a rare entity, diabetic fibrous mastopathy or lymphocytic mastitis is a benign complication that should be included in the differential diagnosis of palpable breast lesions in pre-menopausal young insulin-dependent diabetic women. Medical history along with typical findings on physical examination and imaging techniques allows a high clinical suspicion.

Breast cancer is its main differential diagnosis. Because of clinical and radiological similarities between both entities, histopathological confirmation will be necessary to establish diagnostic certainty, and ultrasound-guided core biopsy is adequate to reach this objective.
References


