Original paper

Diabetic Mastopathy In Iraqi patients; Modalities Of Diagnosis And Management Options

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Abstract

Background: Diabetic fibrous mastopathy, also known as lymphocytic mastitis, is an un common lesion of the breast that occurs in women with long standing insulin dependent diabetes mellitus (IDDM)
It is a distinct clinicopathologic entity with specific histopathological characteristics, which include keloid fibrosis, epithelioid fibroblast, widespread periductal/lobular lymphocytic infiltration and widespread perivascular lymphocytic infiltration.
Objective: To confirm that: (a) Many diabetic patients can be spared from undergoing multiple, unwarranted surgical biopsies (b) Mastopathy can happen even in NIDDM, (c) Diabetic mastopathy can co-exist with malignant breast lesions.
Patients And Methods: A study for 48 patients with palpable breast masses. The patients are divided into 3 groups: Group A (10 patients): contain the patients with long standing IDDM. Group B (14 patients): contain the patients with NIDDM. Group C (24 patients): contain age matched control non-diabetic patients selected with clinical finding similar to that present in diabetic mastopathy. FNAC, ultrasound and mammographic examinations were done before proceeding for excisional biopsy.
Results & Discussion: We found that 7 out of 10 patients in Group A (70%) have features suggesting of diabetic mastopathy and only 4 out of 14 patients in group B (28.5%) and (0%) in group C, have the same features. So we demonstrate that, diabetic mastopathy could be the only cause of palpable breast mass in diabetic patients.
Diabetic mastopathy is a distinct clinicopathologic entity with specific histopathological features, which include keloid fibrosis, epithelioid fibroblast, widespread Periductal/lobular lymphocytic infiltration and widespread perivascular lymphocytic infiltration. Our work confirmed the presence of the histopathological characteristics of diabetic mastopathy in palpable breast masses in long standing IDDM (group A). We also observed the presence of the histopathological characteristics of diabetic mastopathy in breast tissue in mastectomy specimens away from intraductal and infiltrating ductal carcinoma in NIDDM (group B).
Conclusion: we should have awareness that this entity exists and a careful correlation of the patient history with physical, radiological and cytological examination should be applied.

Keywords: Diabetic mastopathy, fibrous mastopathy, lymphocytic lobulitis.

Introduction

Diabetic fibrous mastopathy, also known as lymphocytic mastitis, is an un common lesion of the breast that occurs in women with long standing insulin dependent diabetes mellitus (IDDM) [1].

It is a distinct clinicopathologic entity with specific histopathological characteristics, which include keloid fibrosis, epithelioid fibroblast, widespread periductal/lobular lympho-

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cytic infiltration and widespread perivascular lymphocytic infiltration [2].

Until a few years ago, none of the numerous complications that may be attributed to insulin dependent diabetes mellitus has been referred to the breast. Only asymptomatic vasculitis is reported as occasional finding of surgical biopsies [3].

One of the first papers indicating the breast as the site of diabetic lesions was produced by Soler and Khardori [4] who in 1984 described a particular fibrous dysplasia of the breast with cheiroarithropathy or autoimmune thyroiditis. Since then, other reports[1-5] have shown how diabetic fibrous breast disease (DFBD) in patients with IDDM may be considered a distinctive clinical entity.

Although not yet univocally defined, the minimum criteria for establishing the diagnosis of DFBD, according to Logan and Hoffman [6], are the following:

-Patient history: early onset, long standing, insulin dependent diabetes mellitus and premenopausal age.

-Physical examination findings: rock-hard, painless, irregularly outlined, discrete, freely movable masses, often bilateral and occasionally solitary.

-Ultrasound findings: mass with marked acoustical shadowing of sound waves (Fig. 1).

-Mammographic findings: dense glandular tissue (Fig. 2).

-Fine needle aspiration cytology findings: rock-hard tissue resisting needle motion, no evidence of malignancy, and insufficient cellular material for evaluation in (50%) of the cases [7]. Diabetic mastopathy involves a hard, irregular, movable, nontender, single or multiple, unilateral or bilateral mass. Mammographic appearances show the presence of a dense parenchymal structure with no distortions or microcalcifications [7]. Ultrasound findings vary from irregular hypoechoic mass with marked acoustic shadowing to a vague hypoechoic area without shadowing [7]. However no discrete solid or cystic masses were identified. Lymphatic infiltration in diabetic mastopathy consists predominantly of B-cells, in contrast to non-diabetic mastitis in which lymphocytic infiltration consists mostly of T-cells. This B-cell predominance is similar to the lymphocytic infiltrate seen in other autoimmune disorders, such as Hashimoto's thyroiditis and benign lymphoepithelial lesion of salivary gland [8]. Although the pathogenesis is still obscure and could be multifactorial, it is generally believed that these lesions are attributable to extracellular matrix expansion secondary to increased collagen production and decreased degradation, in part related to the hyperglycemic state. Another reason is autoimmune reaction, showing lymphocytic infiltration for B cells [9].

Histologic findings are necessary for the diagnosis of diabetic mastopathy, but fine needle aspiration cytology cannot obtain sufficient material for a diagnosis because of the hard tumor. Core needle biopsy is recommended to avoid unnecessary surgical procedure because surgery may exacerbates the condition.

Objective

To confirm that:

I. Many diabetic patients can be spared from undergoing multiple, unwarranted surgical biopsies.

II. Mastopathy can happen even in NIDDM.

III. Diabetic mastopathy can co-exist with malignant breast lesions.

Patients and Methods

Twenty four diabetic female patients had been admitted to Medical city hospital in the period between January 2000 and January 2003, complaining of palpable breast masses. Another 24 non diabetic patients were selected as a control group.

The patients are divided into 3 groups:

Group A (10 patients): contain the patients with long standing IDDM.

Group B (14 patients): contain the patients with NIDDM.

Group C (24 patients): contain age matched control non-diabetic patients selected with clinical finding similar to that present in diabetic mastopathy.

FNAC, ultrasound and mammographic examinations were done before proceeding for excisional biopsy.

Analysis for the clinical and histopathological findings was done.

Results

The age of the 10 patients in group A were ranged between 35-63 years with a mean of 44 years. On physical examination, every patient had one or more painless, non-tender, rock-hard, irregularly outlined and freely movable masses without fixation to the skin usually present from 1-6 months before the initial visit. The masses were frequently multiple (7 out of 10 patients). The lesions were found equally in all four quadrants, their positions often were bilaterally symmetrical but their sizes varied between 5mm-6cm.

All but two of the patients were premenopausal and there was an impression of low fertility among these women, the total parity was 14 children in 10 patients.

None of the patients noted rapid change in size of the mass, neither following its' discovery, nor with menses. Only two women gave a history of having taken contraceptive pills.

None of the patients had nipple discharge.

FNAC showed unusually firm –to-hard resistance to the in-and-out motion of the needle used, which is not observed in any other benign or malignant conditions. This resulted in insufficient material for evaluation. The findings were cytological benign ductal epithelium and fibro fatty tissue.

Ultrasound findings of the patients were more indicative, showed marked acoustic shadowing even more than noted with most cancers of the breast (Fig.1).

Mammography was done; the lesion appeared mainly as homogenous opaque mass with poorly defined limits without micro calcifications (Fig.2).

Eight of the patients in group A had systemic complications from long standing IDDM (Table 1).

Table 1: Group A, clinical data.

Pt	Age(year)	Duration of diabetes (year)	Complications
1	45	10	Peripheral vascular disease
2	44	11	Neuropathy
3	37	12	-
4	39	15	Peripheral neuropathy, 5th toe amputation
5	46	9	Diabetic foot ulceration
6	50	11	Retinopathy
7	63	7	Retinopathy
8	35	9	-
9	40	12	-
10	41	10	Nephropathy

In group A, 3 of the patients (30%) demonstrated all the histopathological features of diabetic mastopathy (keloid fibrosis, epithelioid fibroblast, wide-

spread periductal/lobular lymphocytic infiltration and widespread perivascular lymphocytic infiltration) (Fig.3).

Keliod fibrosis (KF) was prominent and accounted for the clinically palpable mass.

Two patients showed 3 out of 4 features and another two patients showed only 2 out of 4 features and the last three patients showed features consistent with fibro adenoma (Table 2).

Table 2: Group A, histopathological findings.

Pt	KF	EF	PDLI	PVLI	Others
1	+	+	+	+	
2	+	-	-	-	Fibro adenoma
3	+	+	+	+	
4	+	+	+	+	
5	-	-	-	-	Fibro adenoma
6	-	+	+	+	
7	+	+	-	+	
8	-	-	-	-	Fibro adenoma
9	-	+	+	-	
10	-	+	-	+	

In group B, the age was ranging from 46-60 years with a mean of 51.5 years, presented with breast masses of variable sizes. The FNAC, u/s and mammographic examination reveal benign lesions in 11 patients and suspicious findings in 3 patients.

In group C, the age was ranging from 35-63 years and they presented with multiple breast masses.

On investigations, these masses were found to be of benign origin in 19 patients and the remainders were suspicious of malignancy.

In group B, only two patients demonstrated 3 of the histopathological features, while another two showed only 2 of the features and another three patients showed features of infiltrating ductal carcinoma with histopathological findings of diabetic mastopathy away from the carcinomatous growth in one of them with the last 7 patients showed benign pathology (Table 3).

Table 3: Group B, clinical and histopathological findings.

Pt	Age(year)	Duration of DM(year)	KF	EF	PDLI	PVLI	Others
1	48	10	+	+	-	-	
2	50	15	-	-	-	-	
3	55	20	-	-	-	-	
4	46	13	-	+	+	-	
5	57	18	+	-	-	+	Ca
6	60	22	-	-	-	-	
7	47	11	-	+	+	+	
8	48	9	-	-	-	-	
9	50	10	-	-	-	-	
10	52	11	-	-	-	-	
11	58	15	-	-	-	-	Ca
12	57	8	-	+	+	+	
13	46	4	-	-	-	-	Ca
14	47	7	-	-	-	-	

In group C, none of the patients had evidence of keloid fibrosis or epithelioid fibroblast while 8 of the control patients had focal periductal/lobular lymphocytic infiltration (PDLI) and another 7 patients had focal perivascular lymphocytic infiltration (PVLI).

Widespread periductal/lobular

lymphocytic infiltration and perivascular lymphocytic infiltration as noted in the diabetic group A, were not present in the control patients.

Only 5 patients with suspicious findings on investigations were proved to have intraductal carcinoma. All the others have benign pathology.

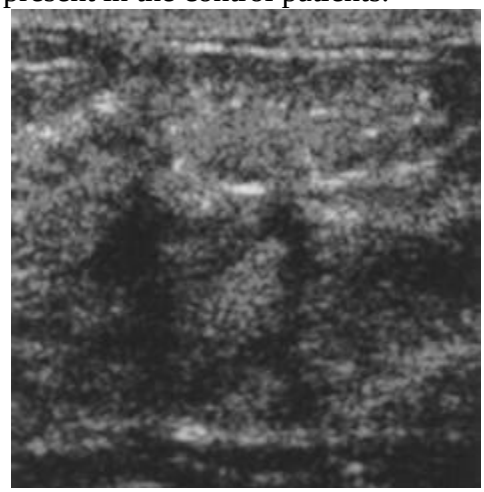

Figure 1

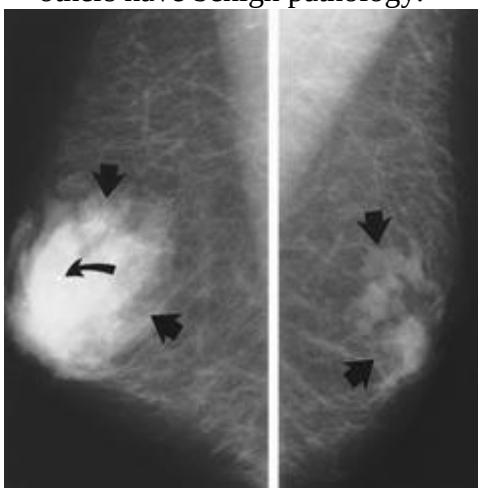

Figure 2

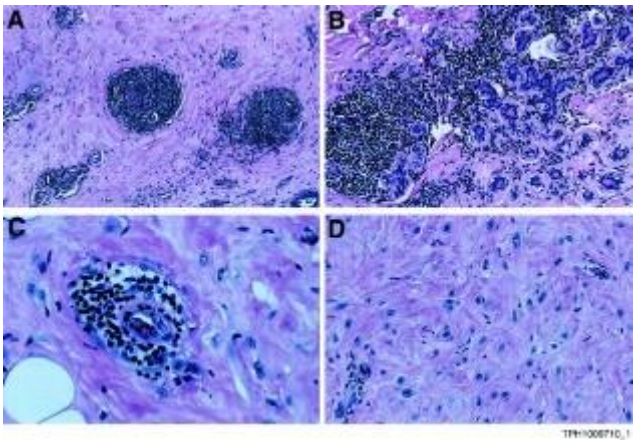

Figure 3:
A: Marked lobulitis with expansion of the collagenous stroma with keloidal features. Note the sharp circumscription of the lymphocytic infiltrate which distinguishes this from chronic nonspecific mastitis.
B: Dense lymphoid infiltrate around the lobular unit which is atrophic.
C: A perivascular infiltrate of mature lymphocytes.
D: Prominent myofibroblast characterized by large, ovoid nuclei and abundant cytoplasm, are dispersed in the keloid-like stroma. These myofibroblast have a characteristic epithelioid appearance.

Discussion

Diabetic mastopathy is a distinct clinicopathologic entity with specific histopathological features, which include keloid fibrosis, epithelioid fibroblast, widespread
Periductal/lobular lymphocytic infiltration and widespread perivascular lymphocytic infiltration [8]. All reports to date had described the features of diabetic mastopathy in palpable breast masses excised from IDDM [10].

The association of diabetes with breast masses and lymphocytic

infiltration was first described by Soler and Khardori in 1984 [4].
They suggested that connective tissue abnormalities observed in diabetes or autoimmunity were speculated as aetiological factors.
HLA histocompatibility typing did not indicate that these patients formed a distinct subgroup of type 1 diabetes [10].
Byrd *et al* confirmed that report of Soler and Khardori by evaluating 11 biopsies from 8 patients with IDDM, the lesion was histopathologically characterized by dense fibrotic tissue and a perivascular lymphocytic infiltration.
The aetiology of this lesion, which they coined "diabetic mastopathy", was speculated to be related to collagen cross-linking and was perhaps a function of aging.
Logan *et al* identified 36 women with long standing IDDM, palpable breast masses and radio graphically dense mammary glandular tissue.
They recommended that patients meeting certain criteria may be monitored with serial FNAC procedures to prevent them from undergoing multiple surgical biopsies.
They also suggested that the mammographic findings of dense glandular tissue in the proper clinical setting is the most consistent finding in diabetic mastopathy, our review of mammographic findings did not, however, yield any consistent findings.
Foschini *et al* described two cases of fibrous mastopathy associated with type 1 diabetes mellitus in patients who presented with breast masses. An autoimmune aetiology was not favored, as none of their patients suffered from an autoimmune disease.
In 1992, Tomaszewski described such an entity with a control group of non-diabetic or short duration diabetic patients with the histopathological findings of fibrosis and chronic mastitis and he suggested that the presence of epithelioid fibroblast was considered to be diagnostic of diabetic mastopathy.
They also suggested that advanced glycosylated end product-related antibody formation as a sequel to glucose-induced matrix expansion is one hypothesis that would explain the combined findings of increase abnormal collagen and lymphocytic mastitis in diabetic mastopathy.
The lack of cysts and characteristic findings of a distinct, non-tender lesion in an otherwise smooth breast clearly distinguishes the lesion from fibrocystic disease.
Rollins suggested that FNAC can be employed as an accurate, rapid and cost effective method for diagnosis as well as for following patients with known diabetic mastopathy to determine whether other nodules that may develop are malignant or benign.
While Pluchinotta *et al* showed that the value of FNAC is limited, even in the absence of atypia, the presence of necrotic elements arouses suspicion.
In this study, FNAC couldn't differentiate between DFBD cases and other benign breast lesions. None of the cases were diagnosed by this technique alone.
Our work confirmed the presence of the histopathological characteristics of diabetic mastopathy in palpable breast masses in long standing IDDM (group A).
In addition, we observed the presence of the histopathological characteristics of diabetic mastopathy in breast tissue in mastectomy specimens away from intraductal and infiltrating ductal carcinoma in NIDDM (group B). This observation is in agreement with that of Page and Mills.
Focal periductal/lobular lymphocytic infiltration and perivascular lympho-cytic infiltration "involving one duct/lobule or vessel" rather than widespread infiltration were observed

in the control population and in our opinion, are non-specific to be helpful in suggesting the presence of diabetes mellitus.

The number of the histopathological characteristics of diabetic mastopathy didn't correlate with the duration of diabetes mellitus.

In this study we also compared the findings to an age-matched control group to further define the specificity of the histopathological findings of diabetic mastopathy.

It is, however, important to recognize that perhaps similar histopathological features may be observed in diabetic and non-diabetic patients with evidence of autoimmune disease, mainly sclerosing lymphocytic lobulitis [15], but the lymphocytic infiltration in this lesion is usually intense, lobulocentric and may form germinal centers [16].

The specificity of these features has been questioned because identical findings were occasionally seen in non-diabetic patients

The only finding was that, the lymphocytic infiltrate in non-diabetic patients is composed predominantly of T-cells, while it is of B-cells in diabetic fibrous breast disease [17].

A case of diabetic mastopathy in 44 years old male with an IDDM of long duration was described, the patient presented with poorly defined nodule in the left breast and the biopsy showed the typical histopathological findings of diabetic mastopathy [19].

Although all of our patients in this study have longstanding diabetes mellitus, Lukas reported a case which had newly diagnosed type I diabetes without retinopathy, nephropathy or neuropathy.

None of our diabetic or control patients had been known to have an autoimmune disease; however, extensive workup for various auto antibodies was not performed.

The association with autoimmune diseases such as Hashimoto's thyroiditis and benign lymphoepithelial lesions of salivary glands, however, may only be apparent as the infiltration in these conditions is of T-cells origin, whereas that in diabetic mastopathy and autoimmune related breast lesion is predominantly composed of B-cells [20].

A lymphocytic rich inflammatory infiltrate, often intense (insulitis), is frequently observed in the islets if patients with type I diabetes early in the course of clinically manifested disease.

The infiltrate is consisted mostly of CD8 T-lymphocytes with variable numbers of CD4 T-lymphocytes.

These T-lymphocytes will lead to local production of cytokines which will lead to expression of class II HLA molecules (T-cell mediated autoimmuneity) [21].

It is, however, evident that the histopathological manifestations of diabetic mastopathy may be a visual summation of many processes including autoimmune diseases that should be investigated also.

Further studies analyzing potential autoimmune targets and characterizing the abnormal matrix component in breast tissue of patients with diabetic mastopathy is needed in order to resolve these issues.

Conclusion

We may consider the possibility of DFBD in young patients who have long standing IDDM with ill-defined mammary thickening of hard consistency but without radiological micro calcifications. The presence of suspicious clinical and imaging, cytological elements that are precarious of malignancy generally suggest the need for surgical biopsy or at least close follow-up.

Although some cases of non-diabetic breast disease may show lymphocytic lobulitis and ductitis or vasculitis or both, EF appears to present only in DFBD.

Finally, we should have awareness that this entity exists and a careful correlation of the patient history with physical, radiological and cytological examination should be applied.

Recommendations

DFBD must be suspected in those patients affected by IDDM and sometimes even in young age, NIDDM for many years with no mammographic calcifications especially if the lesions are fairly large and found in multiple locations.

Although FNAC is difficult to perform, but by itself aids in the diagnosis and can spare the patient from multiple surgical biopsies especially in the follow-up of a known case of DFBD.

For patients presented with DFBD, we recommend the following:-

-In patients under the age of 25 years, we don't perform mammography; we only monitor these patients with regular physical examinations, sonography and FNAC.

-In patients between 25-30 years old, we obtain a baseline mammography and follow-up changing breast masses with sonography and FNAC.

-In older women, we advise to undergo yearly physical, sonographic and mammographic examinations because the number and size of diabetic fibrous masses usually increase as the patient grows older.

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