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CLINICAL & BASIC RESEARCH

Idiopathic Granulomatous Mastitis

Diagnostic strategy and therapeutic implications in Omani patients

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التهاب الثدي الحبيبي

خطط التشخيص و التطبيقات العلاجية للمرضى العمانيين

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الملخص: **الهدف**: يعتبر إلتهاب الثدي الحبيبي مرض حميد ونادر يصيب الثدي لأسباب مجهوله، وعادة ما يتم تشخيصه بشكل خاطىء سريريا وإشعاعيا على أنه ورم خبيث في الثدي، ونتيجة لذلك قد تتم معالجته بشكل خاطىء. وعلى الرغم من عدم وجود طريقة ثابته لعلاج هذا المرض المزمن، إلا انه قد تمت تجربة العلاج بالجراحة أو بإستخدام أو (كورتيكوستيرويد) أو العلاج الكيمياوي. وقد ظهرت نتائج مثيرة للجدل في أغلب الدراسات. **الطريقة**: قد قامت وحدة أمراض الثدي بمستشفي جامعة السلطان قابوس بعمل دراسة سريريه شملت عشرون مريضة مصابة بورم الثدي حيث أثبتت الفحوصات السريرية والإشعاعية أن المرض خبيث، وقد تم تشخيصه على أنه إلتهاب ثدي حبيبي فقط من خلال التشريح النسيجي. في هذه الدراسة سنناقش البيانات السريرية، والتشخيص ومتابعة حالة المرض، و فرص عودة المرض وبيانات المتابعة للمريضات مع مراجعة المراجع العلمية ذات الصلة بهذا الموضوع. **النتائج**: إن غالبية الحالات لمرضانا هي حالات فردية لأسباب غير معروفة وقد ظهرت على شكل كتلة في أحدى الثديين. وقد ظهر لبعض المريضات كتلة في الثدي مع خراج يصاحبه تضخم في العقد اللمفاوية. لقد ثبت إشعاعيا إصابة أربع من المريضات بورم خبيث. أرسل الصديد للزراعة. وكانت النتيجة عدم وجود بكتيريا. وقد أظهر الفحص المجهري الصفات المميزة لالتهاب الثدي الحبيبي. وقد خضعت جميع المريضات للعلاج باستخدام المضادات الحيوية لمدة ستة أسابيع و كان متوسط متابعة المريضات لمدة 15 شهرا (11–33 شهرا). وقد أظهرت جميع المريضات تقلص تام مع عدم ظهور جديد للمرض. وقد أظهرت واحدة من المريضات رجوع للمرض ولكنها استجابت للعلاج بمزيد من المضاد الحيوي. **الخلاصة**: أن هذه الدراسة الموسعة والمفردة على حالات إلتهاب الثدي الحبيبي في عمان قد سلطت الضوء على الأخطاء في تشخيص هذا النوع غير الورمي وغير معروف الأسباب . وقد أكدت الدراسة على الإستجابة الممتازة للعلاج بالمضادات الحيوية لإلتهاب الثدي الحبيبي الذي طالما أعتبر مرضا يصعب علاجه ومثارا للجدل.

مفتاح الكلمات: التهاب الثدي الحبيبي؛ التشريح النسيجي؛ المناعة الكيميائية؛ أشعة الثدي؛ الأشعة التلفزيونية؛ التشخيص؛ مضادات حيوية.

abstract: ***Objectives:*** Idiopathic granulomatous mastitis (IGM) is a rare benign disorder of the breast whose aetiology is controversial, and is often misdiagnosed clinically and radiologically as mammary malignancy; as a result, it may be incorrectly treated. Although no standard treatment is available for this chronic disease, surgery with or without corticosteroids has been tried with controversial results. This study discusses the clinical presentation, diagnosis, management, recurrence, and follow-up data of IGM with a review of relevant literature. ***Methods:*** From 2009–2012, the Breast Unit at Sultan Qaboos University Hospital, Oman, conducted a clinical study on 20 patients with breast lumps. Their clinical and radiological examinations were indeterminate, and a diagnosis of granulomatous mastitis was established only by histopathology. ***Results:*** The majority of the patients were cases of unknown aetiology, who presented with a unilateral breast mass. A few patients had a mass with an abscess, along with axillary lymphadenopathy. A total of 4 patients were suspected of malignancy using radiology. In all patients, sterilised pus was sent for culture and sensitivity. Microscopy showed the characteristic pattern of granulomatous inflammation. All patients were treated with antibiotics for 6 weeks, and the mean follow-up period was 15 months (11–33 months). All patients had complete remission with no further recurrence. ***Conclusion:*** This single largest study of cases of IGM in Oman highlights the pitfalls in diagnosing this non-neoplastic disease of unknown aetiology and uncertain pathogenesis. It emphasises IGM's excellent response to antibiotics, which is crucial, as IGM is a disease which is notoriously difficult and controversial to treat.

Keywords: Breast; Granulomatous Mastitis; Pathology; Immunohistochemistry; Mammography; Ultrasonography; Diagnosis; Antibiotics; Oman.

Advances in Knowledge

- *Idiopathic granulomatous mastitis can mimic a breast carcinoma; it is hence vital, when treating patients, not to ignore the clinical, radiological and histopathological findings of this rare, though benign, challenging disease.*

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- *The use of broad-spectrum antibiotics may provide gratifying results in selected groups of patients, thus obviating the need for surgery and immunosuppressive drugs.*

Application to patient care

- *This study shows that conservative management of idiopathic granulomatous mastitis can prevent needless surgeries and the use of immunosuppressive agents, thereby decreasing morbidity.*

Idiopathic granulomatous mastitis (IGM) is a rare benign disorder of the breast first described in 1972 by Kessler and Wolloch.[1] Most patients are women of childbearing age with a recent history of pregnancy and lactation.[2] Patients present with a unilateral painful breast lump, with no predilection to a particular quadrant. In most cases, there is no axillary lymph node involvement. Although the exact aetiology of IGM remains unclear, associations with autoimmune disorders, oral contraceptive use, pregnancy, hyperprolactinaemia and alpha-1 antitrypsin deficiency have been suggested.[3] Diagnosis of IGM is also very challenging as the clinical and radiological features often mimic a carcinoma.[4] The definitive diagnosis is usually established by histopathology. Although there is no clear clinical consensus regarding the ideal therapeutic management of IGM, wide local excision and corticosteroids are commonly used to treat this condition, albeit with a very high local recurrence rate.[5] This article discusses the clinical presentation, diagnosis and management of 20 cases of IGM at Sultan Qaboos University Hospital (SQUH), a secondary care teaching hospital in Oman.

Methods

A prospective study was undertaken of 20 patients diagnosed with IGM and treated in SQUH from 2009 to 2012. Female patients of all ages presenting with clinical features of breast lumps, with or without primary breast abscesses, were included in the study. The diagnosis of IGM was based on core biopsy using a Bard® disposable 14 gauge core biopsy needle (Bard Biopsy Systems, Tempe, Arizona, USA). The biopsy was sent for immunohistochemistry, for pancytokeratin and epithelial cadherin (E-cadherin) staining, and the pus was sent for microscopy, culture and antibiotic sensitivity. All patients diagnosed with IGM were managed conservatively with systemic antibiotics consisting of augmentin (1 gm twice a day) for 6 weeks and metronidazole (400 mg three times a day) for two weeks. Patients who developed secondary breast abscesses had fine needle aspiration (FNAC) and a further course of antibiotics for another two weeks. Patients with previous surgery or medical treatment for chronic diseases, chronic mastitis, non-granulomatous mastitis, immunocompromised patients, and those allergic to the penicillin group of drugs were excluded from the study. Ethical clearance was obtained from the SQUH ethics committee. The data were entered into a predesigned proforma with the following variables: clinical presentation, radiological imaging, microbiological findings, histopathological assessment, treatment modalities, recurrence, and follow-up. The data were analysed using descriptive statistics.

Results

This study reports 20 patients who presented with a breast lump at the Breast Unit of Sultan Qaboos University Hospital (SQUH); all patients underwent triple assessment (clinical, radiological and histopathological) to establish the diagnosis of GM.

The clinical characteristics of the cases were as follows: 20 patients presented with a breast lump, ranging from 2–10 cm (mean size 5.6 cm), and manifesting as firm, tender, ill-defined and indurated. The lesions were unilateral. The right breast was affected in 12 cases (60%) and the left breast in 8 cases (40%), with most of the lumps centrally located around the areola. Only one patient developed a lump in the contralateral breast 5 months after treatment, and the biopsy from the lump was suggestive of GM. Three of the patients (15%) presented with primary breast abscesses and 6 patients (30%) presented with secondary abscesses. A total of 13 of our patients (65%) had axillary lymphadenopathy, where the lymph nodes were firm and fixed with a mean size of 1.8 cm. Two patients (10%) had nipple retraction, two patients (10%) presented with nipple discharge

Table 1: Clinicopathological characteristics of patients

Characteristic	Number of cases 20 (%)
Age (years)	
<40	14 (70)
>40	6 (30)
Parity	
Nulliparous	0
Multiparous	20 (100)
Breastfeeding	
Yes	20 (100)
No	0
Oral contraceptives	
Yes	2 (10)
No	18 (90)
Clinical presentation	
Pain	20 (100)
Right breast lump	12 (60)
Left breast lump	8 (40)
Nipple retraction	2 (10)
Nipple discharge	2 (10)
Peau d'orange	1 (5)
Axillary lymph nodes	13 (65)
Radiological imaging	
BI-RAD IV	1 (5)
BI-RAD V	3 (15)
Microbiology	
Organisms absent	20 (100)
Histopathology	
IGM	19 (95)
Indeterminate	1 (5)
Treatment	
Antibiotics	19 (95)
Surgery	1 (5)
Recurrence	**0**
Follow-up	
<1 year	6 (30)
>1 year	14 (70)

BI-RADS = Breast Imaging Reporting and Data System; IGM = idiopathic granulomatous mastitis.

and one patient presented with *peau d'orange*, a pitted or dimpled appearance of the skin which is characteristic of some types of breast cancer. The majority of our patients were of childbearing age (25–54 years), with a mean age of 37.5 years, and all of them were multiparous (mean = 4 children) and had breastfed their children. Two of them (10%) had a history of taking hormonal contraceptives [Table 1].

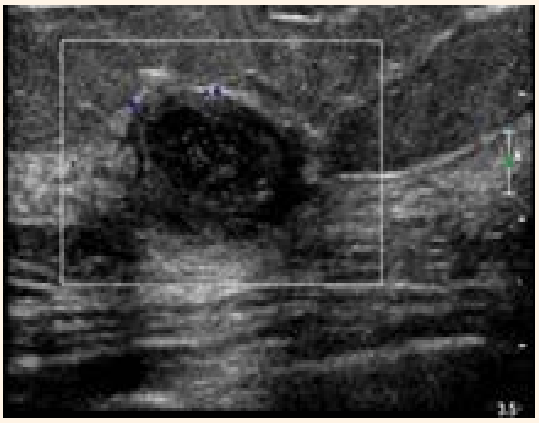

Figure 1: Ultrasound showing an irregular mass with both solid and cystic components.

The radiological features of the cases were determined through ultrasound and mammography. An ultrasound was performed in all 20 cases, with both a mammogram and an ultrasound done in the 7 cases (35%) which showed dilated ducts with thick debris, or cystic lesions with debris, or severe inflammatory changes [Figure 1]. The lesions ranged from 1–7cm. In 4 of the patients (20%), a hypoechoic mass was seen on the ultrasound. The majority of the masses under mammography did not show any calcification, spiculation or changes involving the skin or nipple. However, in one case some skin-thickening was seen in the region of the skin and areola, and the nipple was retracted. In 4 patients (20%), radiological findings were suspicious of malignancy. Several patients were graded using the Breast Imaging Reporting and Data System (BI-RADS); three patients were graded as BI-RADS V and one patient as BI-RADS IV.[6]

The histological and cytological characteristics of the cases were determined by FNAC, which was suggestive of IGM in 5 patients (25%), and was inconclusive for the others. All patients underwent core biopsy regardless of FNAC-confirmed IGM. In one patient, core biopsy was inconclusive for IGM, so an open biopsy was done which, by cytology, was suggestive of IGM. The sensitivity of core biopsy was 95%. All other cases on histopathology showed

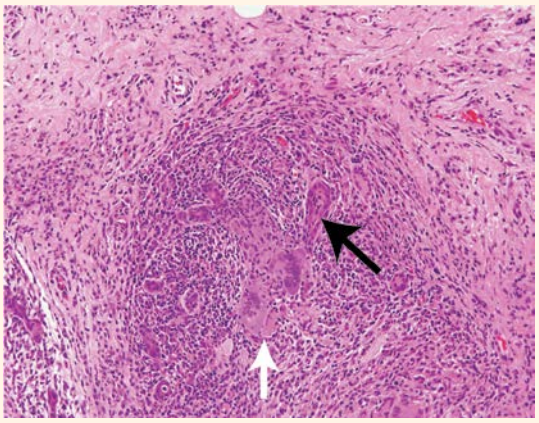

Figure 2: Breast lobule under haematoxylin and eosin stain and x 100 magnification, showing expansion due to a granulomatous inflammation.

moderate to severe lobule-centric non-caseating granulomatous inflammation, involving most of the lobules in a global fashion, with a sparing of the ducts and the absence of fat necrosis in all of the biopsies. The necrotising granulomas comprised collections of granulocytes (predominantly neutrophils), lymphocytes and plasma cells, palisaded by sheets of epithelioid cells and foreign body giant cells with intact acini, or acini showing destruction [Figure 2]. Pancytokeratin and E-cadherin staining confirmed the lobular localisation of the granulomas and the progressive destruction of the *acini*. In one case, the severely inflamed lobule showed ectatic *acini* containing necrotic inspissated material. Two of the cases were suggestive of duct ectasia with GM. None of the cases showed caseating granulomas suggestive of tuberculosis. Gram, periodic acid-Schiff, Ziehl-Neelsen and Giemsa stains did not reveal any microorganisms (bacteria, mycobacteria, fungi and parasites).

In the subsequent treatment and follow-up of the cases, there was significant improvement in 17 out of 20 patients (85%) treated conservatively with antibiotics. Surgical treatment with wide local excision was performed in one patient where the diagnosis could not be confirmed either radiologically or by core biopsy. Two patients were lost to follow-up after the initial treatment. Post-treatment response was monitored both clinically and radiologically with a breast ultrasound every 3 months. A total of 6 patients had secondary abscess formation (initially presenting with a hard mass) within the first 3 months, and these patients had FNAC of the abscess and were given antibiotics for a further two weeks. After a mean follow-up at 15 months (11–33 months), there was no recurrence in 18 out of the 20 patients and all of them are in complete remission to date.

Discussion

IGM is an uncommon clinical condition involving the breast. Though the exact aetiology of this condition is not known, an autoimmune reaction to the protein secretions from the mammary ducts is implicated in its causation.[7] Histologically, IGM is characterised by the presence of non-necrotic granulomas confined to breast lobules. As the radiological and clinical features closely mimic a carcinoma in most instances, IGM often poses a diagnostic and therapeutic dilemma. IGM has been reported to occur commonly in women of reproductive age,[8] and this has been seen in our study, wherein the mean age of the patients was 37.4 years. Typically, IGM presents as a breast mass; pain, skin-thickening, abscess formation, sinus or regional lymphadenopathy may be associated features.[8]

Thus, when women with IGM present with a hard unilateral mass, axillary lymphadenopathy, nipple retraction or *peau d'orange*, IGM can be mistaken for a carcinoma.[5] In our study, all of the patients presented with a unilateral mass, which was most often situated in the periphery of the breast. Only one patient developed a *de novo* mass in the contralateral breast a few months after the diagnosis of IGM in the other breast. However, the *de novo* mass was suggestive of IGM when using core biopsy. Similar to other studies, our patients also commonly presented with cellulitis, axillary lymphadenopathy, abscesses, skin-thickening and nipple retraction. Mammographic features of IGM are essentially nonspecific, with focal asymmetric density being the most common feature.[7–11]

Our study showed that the most common radiological findings observed were dilated ducts with inflammatory changes, with some patients (15%) showing cystic lesions with thick debris. Using mammography, 20% of our patients displayed asymmetric diffuse density of fibroglandular tissue and with ultrasound, 20% of the patients showed hypoechoic ill-defined lesions.

With these nonspecific clinical and radiological findings, histopathology played a crucial role in diagnosing the cases of granulomatous lobular mastitis. FNAC for pus aspiration and culture was done in 6 patients (30%) who presented with an abscess, because IGM can mimic an abscess, and FNAC gives faster results than core biopsy. In our study, core biopsy was more accurate than FNAC in diagnosing IGM, as the characteristic features of IGM were more obvious with histopathology. As in the study done by Larsen *et al.*, core biopsy was more accurate as it showed the tissue architecture.[8] Core biopsy was diagnostic in 19 patients (95%), and was indeterminate in only one patient.

Granulomatous lobular mastitis is characterised histologically by the presence of non-necrotising granulomas, usually admixed with neutrophils originating in the breast lobules.[8] The other conditions that can mimic IGM are mammary duct ectasia and chronic inflammatory conditions like plasma cell mastitis, tuberculosis, histoplasmosis, sarcoidosis and Wegener's granuloma.[11] Hence, a biopsy is useful to distinguish IGM from other granulomatous conditions, as well as establishing malignancy. In our study, the cases were characterised by chronic lobulitis with granulomatous inflammation. The granulomas comprised collections of granulocytes (predominantly polymorphs), palisaded by sheets of epithelioid cells and foreign body giant cells. Pancytokeratin and E-cadherin staining confirmed the lobular localisation of the granulomas and the progressive destruction of the *acini*.

The exact causes of IGM are still unknown. Keller and Wolloch proposed an autoimmune pathogenesis.[1] It has been postulated that as most women presenting with IGM are in the reproductive age group, and since many patients had previously given birth or were lactating at the time of the initial symptoms, a localised immune response to extravasated secretions from lobules may occur. Miliauskas *et al*. reported a case in which they showed that immunohistochemical staining of the lesion contained predominantly stromal T lymphocytes.[12] This might be due to a local cellular response to injury as there has been no evidence of systemic immune abnormalities such as the formation of autoantibodies or antigen-antibody complexes.

Furthermore, in our study, no microorganisms (bacteria, mycobacteria, fungi and parasites) were demonstrated by Gram, periodic acid-Schiff, Ziehl-Neelsen or Giemsa stains. Going *et al*. emphasised the importance of use of appropriate swabs and appropriate transport media to recover these organisms.[13] Miles *et al*. reported that immediate inoculation into Robertson's cooked meat broth has been shown to increase the recovery and range of organisms from wound swabs.[14]

The treatment of IGM remains contentious, and there is no clear clinical consensus regarding the ideal therapeutic management of IGM. Although several studies have reported different approaches for the management of IGM, many of these treatment algorithms were formulated without a definitive initial diagnosis.[15] The treatment plan for IGM followed at most centres is to perform a complete resection or an open biopsy with corticosteroid therapy.[16] However, surgery can be complicated by abscess formation, fistulas, scarring and chronic suppuration. Chronic mastitis after excisional biopsies has also been reported.[17] Imoto *et al*. followed 29 patients with IGM, of which 11 (38%) showed relapse, and thus patients must be followed carefully after treatment by excision.[18] Bani-Hani *et al*. reported 24 patients with histologically-confirmed IGM who were treated by wide local excision. Their analysis of patients over a period of 8 years showed a 16% recurrence after a mean follow-up period of 31.2 months.[11] As some studies have implicated an immune aetiology for IGM, many centres have used prednisolone as a common regimen especially with clinically advanced diseases or more severe symptoms. However, high-dose steroids, in addition to their potential side effects, have been linked with a recurrence rate as high as 50%, as seen in one study by Azlina *et al*.[19] Immunosuppressive agents, like methotrexate or azathioprine, have also been utilised, with variable responses, in cases refractory to the above therapies.[20–21] Akbulut *et al*. retrospectively analysed 541 IGM cases treated with steroids and/or methotrexate between 1972 and 2010. They found a high recurrence rate in patients using steroids, and also the occurrence of adverse side effects such as steroid-induced diabetes mellitus. However, in 4 cases exhibiting recurrence, when methotrexate was used instead of steroids, it was found to be more effective in preventing

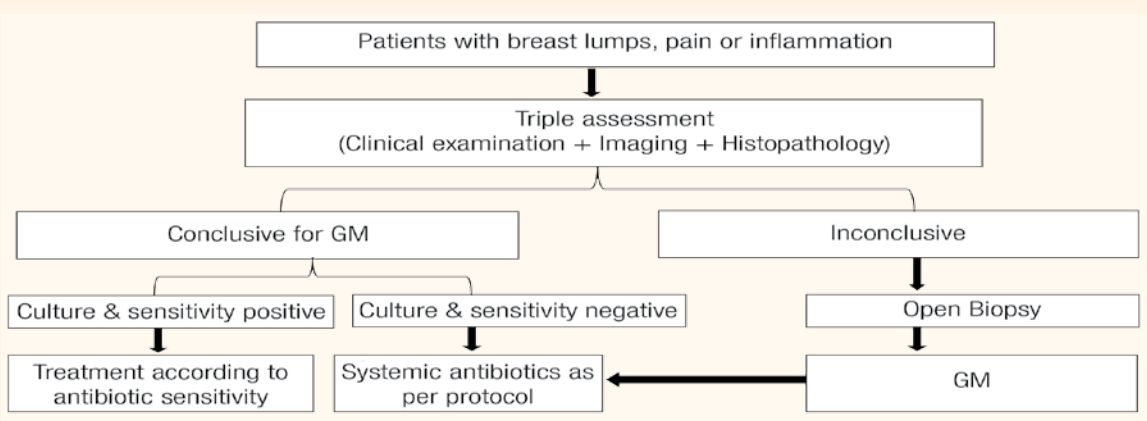

Figure 3: Diagnostic and therapeutic algorithm for patients suspected of granulomatous mastitis at Sultan Qaboos University Hospital, Oman.

GM = granulomatous mastitis.

complications, resolving the inflammatory process, and limiting the side effects of corticosteroids.[22]

Conservative management has been tried by various centres due to the variable responses to different therapeutic strategies. In a study by Lai *et al.*, 8 patients were treated conservatively, with no surgery performed or medication given, and were monitored with close regular surveillance. A total of 50% of the patients had spontaneous complete resolution of disease after a mean interval of 14.5 months.[23] Based on the clinical presentation of the cases and the presence of acute inflammatory cells, the Breast Unit at SQUH developed a diagnostic and treatment algorithm by conservatively managing histopathologically proven cases of IGM [Figure 3]. With this mode of management, all women with IGM showed improvement, excluding the two patients who were lost to follow-up.

Based on the results of our study, the Breast Unit team at SQUH implemented the following treatment plan for women diagnosed with granulomatous lobular mastitis. Initially, a course of antibiotics is prescribed for 6 weeks, with assessment of the patient every 3 months. If there is recurrence, a second course of antibiotics is given. If treatment fails, or if minimal or no improvement is seen after the second course of antibiotics, other options are considered. At SQUH, patients are examined by the breast surgeon at least every two weeks for the first month, then on a monthly basis for the next 3 months. A follow-up ultrasound is performed 6 months after the symptoms have resolved. Thereafter, if the patient is asymptomatic, and imaging does not show any recurrence, the patient is advised to undergo annual screening following the national screening guidelines.[24]

Conclusion

IGM is an enigma because of its nonspecific clinical and radiological characteristics, and poses a diagnostic and therapeutic dilemma to the treating surgeon. Nevertheless, the ultimate diagnosis of this chronic inflammatory disease rests on core biopsy. In our series, treatment with antibiotics produced excellent responses and patients did not require any other forms of treatment. As the course of the disease is unpredictable with a strong tendency towards persistence and recurrence, a conservative approach seems to be the best option in the management of this disease. Greater awareness of the rare entity of IGM is mandatory to avoid unnecessary mastectomies and to reduce morbidity among patients.

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