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Idiopathic granulomatous mastitis. Experience at a cancer center

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ABSTRACT

Background. Idiopathic granulomatous mastitis (IGM) is a benign breast disease that has been described as a rare granulomatous inflammation (GI). It can mimic inflammatory breast cancer. **Material and methods.** We included women with a diagnosis of IGM referred to an oncologic hospital between January 01, 2007 and to March 31, 2011, with diagnosis of breast cancer, in whom biopsy reported GI, without other cause related. The aim of this study was to review the clinical, radiologic and pathologic characteristics of a cohort of women with IGM. **Results.** We analyzed 58 patients; mean age was 38 ± 12 years. Mammography showed diffuse asymmetry (n = 19) and focal asymmetry (n = 13); breast ultrasound showed heterogeneous and hypoechoic areas (n = 28) and lumps (n = 21) as the most frequent lesions. All biopsies showed lobulocentric GI. Treatment included antibiotics (n = 20), steroids (n = 8), both treatments (n = 20), surgical excision (n = 3) and observation (n = 7). Forty-three patients (74%) had complete remission; mean time to remission was 9.5 ± 5.8 months. Fifteen (26%) had partial remission. Any patient had progression or relapse. **Conclusions.** IGM is a benign breast condition that may mimic breast inflammatory cancer. Ultrasonography and mammography findings reveal characteristic data that can be useful for establishing the diagnosis; however, biopsy is the gold standard for its diagnosis and should be taken in any patient even with a mild suspicion of cancer.

Key words. Breast. Benign inflammatory diseases. Idiopathic granulomatous mastitis.

Mastitis granulomatosa. Experiencia en un centro oncológico

RESUMEN

Introducción. *La mastitis granulomatosa idiopática (MGI) es una inflamación granulomatosa (IG), benigna de la mama, cuyo diagnóstico diferencial incluye el cáncer inflamatorio de la mama.* ***Material y métodos.*** *Se presenta un estudio retrospectivo de pacientes con diagnóstico de MGI atendidas en un hospital oncológico de referencia, entre el 1 de enero 2007 y el 31 de marzo 2011 con diagnóstico presuntivo de cáncer de mama, en quienes el reporte histológico fue mastitis granulomatosa; sin identificar otras causas relacionadas. Se revisaron las principales características clínicas, de imagen e histopatológicas.* ***Resultados.*** *Se incluyeron 58 pacientes; la media de edad fue de 38 ± 12 años. La mastografía reportó principalmente asimetría difusa (n = 19) y asimetría focal (n = 13), y el ultrasonido zonas heterogéneas e hipoecoicas (n = 28) y nódulos (n = 21). Todas las biopsias mostraron IG centrada en el lobulillo. El tratamiento incluyó: antibióticos (n = 20), esteroides (n = 8), ambos (n = 20), resección quirúrgica (n = 3) y observación (n = 7). Cuarenta y tres pacientes (74%) cursaron con remisión clínica completa, con una media de 9.5 ± 5.8 meses. En 15 (26%) hubo remisión parcial. No se reportaron casos de progresión o recaída.* ***Conclusiones.*** *La MGI es una patología benigna de mama que puede simular cáncer inflamatorio. El ultrasonido y la mastografía aportan características que orientan al diagnóstico; sin embargo, la biopsia es el estándar de oro y debe realizarse en todo paciente con sospecha de cáncer.*

Palabras clave. *Mama. Patología benigna. Mastitis granulomatosa idiopática.*

BACKGROUND

Idiopathic granulomatous mastitis (IGM) is a benign breast lesion that has been described as a rare, chronic, nonspecific granulomatous process. It is an orphan entity that may be evaluated by many different specialists. It has a protean presentation and diagnosis and treatment has not been standardized.

Since the first report of IGM in 1972 by Kessler and Wolloch, only a few case reports and small series have been published.[1]

The prevalence of IGM is unknown, is characterized by the presence of non-caseating granulomas without any evidence of infection.[1] Diagnosis may be difficult, as well as treatment. Antibiotics, anti-inflammatory drugs and even surgery has been recommended, but currently, there are not established guidelines established for its treatment.

We present the experience of a cohort of patients with IGM seen at a cancer referral center in México City.

MATERIAL AND METHODS

The Instituto Nacional de Cancerología (INCan) is a teaching, cancer referral hospital in México City, México. Six hundred patients with new, palpable or non-palpable breast lesions with BIRADS (Breast Imaging Reporting and Data System) III-V mammographies are seen each year, together follow all these patients. At each clinical visit, information is recorded and coded according to the diagnosis.

We included all women diagnosed with IGM between January 1st, 2007 and March 31st, 2011. Seventy-one patients had histopathological diagnosis of GM. Thirteen patients (18%) were excluded from the study: three, with incomplete information at the electronic medical chart, as they were treated elsewhere, one was male and nine were eliminated after reevaluation by the study pathologist (4 had a positive Ziehl-Nieelsen stain, 1 had vasculitis, 1 had plasma cell mastitis, 2 had a foreign-body reaction, and 1 was diagnosed with ductal ectasia).

Fifty-eight patients were included in the analysis. The histopathological diagnostic criteria included:

- GI with predominant lobular involvement.
- Absence of morphological data suggesting other causes of GI (i.e. fat necrosis, caseous necrosis, vasculitis and sarcoid granulomas, amongst other).
- Negative histochemical stains for fungi, mycobacteria or other bacteria.

The information was retrospectively reviewed using the electronic chart, along with the histopathological and radiological information. Clinical breast

Table 1. Demographic and clinical characteristics of patients with idiopathic granulomatous mastitis (n = 58).

Variable	Total
Breastfeeding,* n (%)	34 (85)
Mean time of breastfeeding history (months) ± S.D.	17 ± 12
Median time of symptoms prior to first hospital visit (months)	2 (range, 0-25)
Breast quadrants, n (%)	
Upper outer	27 (46%)
Upper inner	12 (21%)
Areola	8 (14)
Lower inner	6 (10)
Lower outer	5 (9)
Mean clinical size (cm^2) ± S.D.	5.5 ± 2.7
Symptoms, n (%)	
Pain	39 (67)
Purulent secretion through a skin sinus	34 (59)
Nipple retraction	7 (12)
Lymphadenopathy	38 (66)
Erythema	29 (50)
Fistulae	17 (29)

*Data available in 40 patients.

Table 2. Ultrasonography and mammography findings in patients with idiopathic granulomatous mastitis.

Characteristics	n (%)
Mammography (n = 38)	
Asymmetry (diffuse)	19 (50)
Focal asymmetry	13 (34)
Well-defined lump	4 (11)
Heterogeneous lump	2 (5)
Ultrasonography (n = 52)	
Heterogeneous and hypoechoic areas	28 (54)
≥ 2 lumps	11 (21)
One lump	9 (17)
Simple cyst	2 (4)
Complex cyst	1 (2)
Spiculated lump	1 (2)
BI-RADS classification score*	
3**	1 (3)
4	33 (87)
5	4 (10)

*Breast Imaging Reporting and Data System (BI-RADS). 3: probably benign lesions; 4: suspicious abnormality; 5: highly suggestive of malignancy. Data was calculated in 38 mammographies performed. **Biopsy was carried out on indication by the patient's Physician.

examination was obtained from the medical electronic chart. The number, size, and location of lumps, skin thickening, axillary lymph nodes, pain, abscess, fistulae, nipple retraction, and secretion were recorded. In addition, information on breast ultrasonography, mammograms, chest X-rays, cultures, and tuberculin test findings were registered. Mammograms and breast ultrasounds (US) were reviewed by a Senior Radiologist from the study group. Fifty-four (93%) biopsies were obtained by Trucut and four (7%), by tumor excision. A second Pathologist who also formed part of the study group reassessed biopsies.

Mastitis outcome was evaluated at patients last visit, as complete response (CR), partial response (PR), relapse or progression.

The study protocol was approved by the INCan Institutional Review Board. No informed consent was requested.

Statistical analysis

A database was constructed for the study purposes. Variables were coded for statistical evaluation. We conducted a descriptive analysis. For categorical variables, number and percentage were calculated; for quantitative data, mean and standard deviation (SD) or median and range were used as appropriate.

Table 3. Histopathologic characteristics of patients with idiopathic granulomatous mastitis.

Histopathologic feature	n	(%)
Lobular involvement	58	(100)
Abundant ductal involvement (>50% ducts)	20	(34)
Ductal dilatation (of any degree)	31	(54)
Giant multinucleated cells		
Langhans type	2	(4)
Foreign-body type	31	(54)
Both types	15	(26)
Clear lipoid-like spaces	44	(76)
Abscess/microabscess formation	22	(37)
Necrosis (other than abscess)	2	(4)
Fibrosis	58	(100)
Macrophages with intracytoplasmic, PAS*-positive hyaline globules	27	(47)

*PAS: periodic-acid schiff stain.

The analysis was conducted with STATA (ver. 11; Stata; College Station, TX).

RESULTS

We analyzed 58 patients; mean age was 38 ± 12 years. At clinical evaluation all patients had unilateral disease and left-breast involvement was more frequent (n = 38, 65%). All patients had a palpable mass, 5 (9%) had more than one palpable mass; mean size was 5.4 ± 2.7 cm. Other demographic and clinical characteristics are presented in table 1.

In those patients who presented fistulae or secretion, a culture was taken (n = 29, 51%): 25 were negative; 4 had coagulase-negative *staphylococci*.

Mammography was performed in 38 patients (66%): nineteen (50%) patients had diffuse asymmetry, and 13 (34%) focal asymmetry. Breast US was performed in 52 patients (90%), showing heterogeneous and hypoechoic areas in 28 patients (54%) and lumps in 21 (36%). Data is presented in table 2.

All cases showed lobulocentric GI and granulomas. Other histopathological findings were: areas of fibrosis of variable extent (100%), multinucleated giant cells (84%), clear lipoid-like spaces (76%), abscesses (37%), and necrosis (4%). Calcification was not observed. Gram, PAS, and Ziehl-Neelsen stains for microorganisms were all negative. The main histopathological characteristics are summarized in table 3.

A consistent histopathologic finding in 29 (48%) of our cases was the presence of macrophages with intracytoplasmic Periodic acid-Schiff (PAS)-positive hyaline globules.

Ductal dilation and inflammation were further analyzed to rule out the later diagnosis. Twenty-one cases (34%) showed abundant ductal involvement; and 33 (54%) ducts presented some degree of dilatation. Ducts showing these features were always small. Ductal involvement was more frequent in women with a history of breastfeeding ($p = 0.01$); and ductal ectasia, was observed among patients with fistulae formation during the course of disease ($p = 0.04$).

Forty-one patients (71%) received antibiotics. The most common antibiotic prescribed was ciprofloxacin (n = 26; 65%), followed by amoxicillin/clavulanate (n = 11; 27%) and clindamycin (n = 9; 22%). Eighteen patients received a combination of two antibiotics.

Twenty-eight patients (48%) received prednisone, in 8 (14%) was the only treatment received, and in 20 (34%), steroids were prescribed after antimicrobial treatment. Mean prednisone dose was 40 ± 15 mg, with average treatment duration of 12 ± 6 weeks.

Three patients (5%) underwent surgical excision due to an inconclusive initial biopsy and high suspicion of malignancy. Seven patients (12%) resolved without any treatment.

Forty-three patients (74%) had CR. Mean time to remission was 9.5 ± 5.8 months. Partial remission was achieved in 15 (26%). Any patient had progression or relapse. Patients had an average follow-up of 16.7 ± 13.8 months. Comparison between therapies and outcomes is illustrated in table 4.

DISCUSSION

The prevalence of IGM is unknown. It has been described worldwide in all races and has been associated with breastfeeding, hormonal contraception, and smoking, with a median age of 35 years,[2-6] but has also been described in older women, and in men.[3,7.8] In this series, mean age was similar to other studies, but we had five patients older than 50 years. Previous breastfeeding was present in 83% of patients, but smoking and hormonal contraception was quite low.[1-3] In a similar report from México, only with 16 cases, patients mean age was 41.7 years, and 50% had breastfed in the previous 6 months.[9]

GM is idiopathic or secondary to other causes, including infectious and noninfectious granulomatous lesions in the breast, such as trauma, mammary duct ectasia, foreign-body granulomas, sarcoidosis, histiocytosis, tuberculosis, bacterial *(Corynebacteria* infection), mycotic, and parasitic infections.[3,5,6,9,10,11] Certain etiologic factors such as an autoimmune phenomenon, a chemical reaction associated with oral contraceptive, or an infection related with unidentified pathogens have been postulated as possible mechanisms of disease.[3]

The cases presented in this series were considered idiopathic; no other infection or inflammatory causes were documented.

The symptoms duration vary from a few days to several months.[4] We found that the median time from detecting the lump until patient's first hospital visit was 2 months, similar to other studies.[11] Considering that cancer is a differential diagnosis, this is a significant delay.[11]

IGM typically presents as a unilateral mass that involves any quadrant of the breast, although bilateral disease has been described sporadically.[2,3,8] The lesions are of variable size (from 1-9 cm), and are usually firm, tender, and well defined,[3,7] similar to our findings. We found lymphadenopathy in 65% and nipple retraction in 12% of patients, symptoms that could mimic neoplastic disease.

The most frequent findings described on mammogram and breast ultrasound were asymmetry, either diffuse or focal, and well-circumscribed lumps, similar to other series[3,4] (Figure 1).

Pathological findings include GI centered in mammary lobules and frequently accompanied by multinucleated giant cells and micro-abscess formation.[2,3] The presence of macrophages with intracytoplasmic, PAS-positive hyaline globules, giant multinucleated cells, and clear lipoid-like spaces in areas of inflammation were the most frequent pathological findings in our series (Figure 2).

Table 4. Treatment and outcome of patients with idiopathic granulomatous mastitis (n = 58).

Treatment, n (%)	Complete remission (n = 43)	Partial remission (n = 15)	Total (n = 58)
Observation	4 (7)	3 (5)	7 (12)
Steroids	6 (10)	2 (4)	8 (14)
Antibiotics	14 (24)	6 (10)	20 (34.5)
Antibiotics plus steroids	17 (29)	3 (5)	20 (34.5)
Surgery	2 (4)	1 (2)	3 (5)

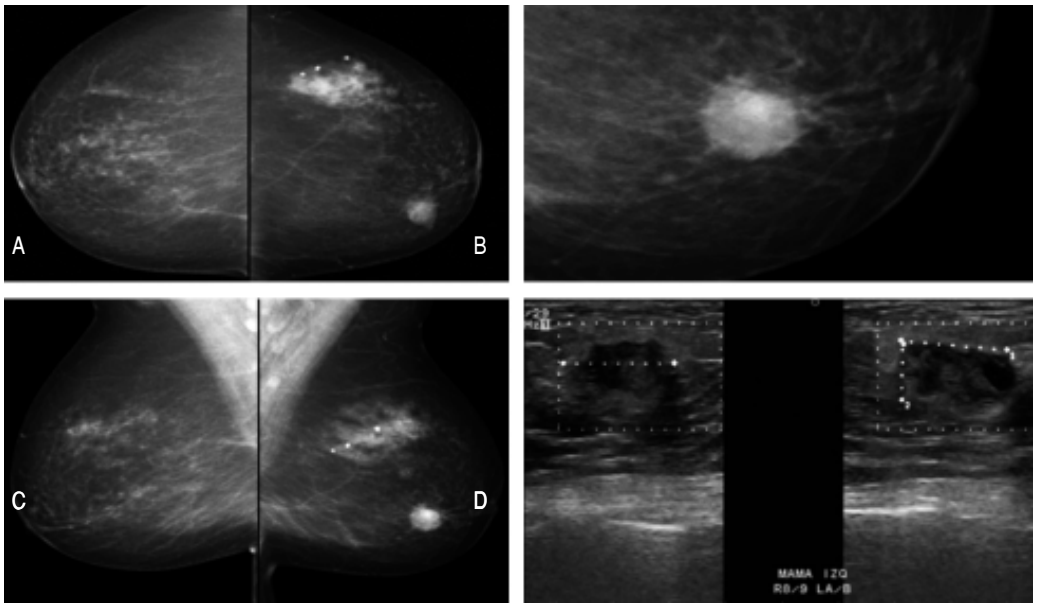

Figure 1. Characteristics of mammography and breast ultrasonography in idiopathic granulomatous mastitis (IGM). A 53-year-old female with IGM. Mammography shows left breast with focal asymmetry, a calcified nodule, and a spiculated nodule localized in the lower inner quadrant. Breast ultrasonography demonstrates an irregular nodule.

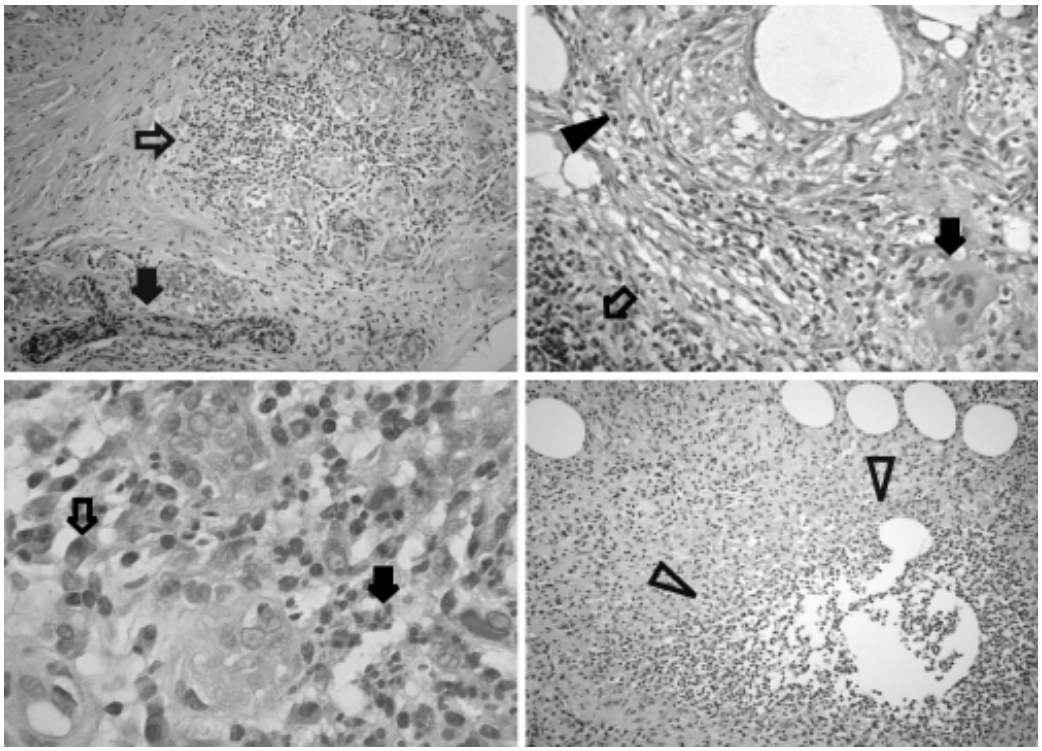

***Figure 2.** Histopathological characteristics in idiopathic granulomatous mastitis. A. Lobular (open arrow) and ductal (solid arrow) involvement. B. Inflammatory granulomatous reaction with central histiocytes (arrow head) and multinucleated giant cells (solid arrow). C. Other inflammatory cells, such as plasma cells (open arrow) and neutrophils (solid arrow). D. Macrophages with hyaline Periodic-Acid Schiff (PAS) stain-positive globules of variable size (arrow head).*

The treatment of IGM remains controversial. A number of therapeutic approaches have been reported, including clinical observation, antibiotics, immunosuppressant treatment (steroids ± methotrexate), and surgery.[3,5] Until revision of this case series, there was not any standard care protocol at our institution, which in part explains the variety in treatments observed in this population.

Antimicrobial treatment was initiated in cases with clinical or microbiological data related to an infectious process, such as purulent secretion through a skin sinus tract, local erythema or hyperthermia, ulceration, fever, or a positive culture.

In low- and middle-income countries such as México, tuberculosis is an important differential diagnosis, particularly when the physician is considering

treatment with steroids. It is important to perform a chest X-ray film and a tuberculin test, and to ascertain a history of contact with patients with tuberculosis or ingestion of unpasteurized milk. Ziehl-Neelsen stain must be performed in biopsy.

Steroids may be associated with long-term symptom control and reduction in lesion size.[5] In this series, 48% of patients received prednisone, none received any other immunosuppressive therapy, as has been described in other studies.[3,5]

Our current practice is to give prednisone (1 mg/kg/day x 2 weeks) with gradual dose tapering in the following 2 months.[3,8,9] Some authors use lower doses (20 mg daily for one month and then a rapid taper), either before or after surgery.[11]

Surgical excision also comprises a treatment modality and can additionally be useful in providing a precise diagnosis. The former has been reported as the most common treatment in other series;[9] is frequently complicated by a high rate of fistula formation, poor wound healing, and anatomical breast disfigurement.[2,3] In this series, surgical excision was performed only in three patients, with CR in two patients; none adverse events were recorded.

Recurrence of IGM has been described as frequent, regardless of the treatment modality.[3,5,12] None of the patients in this series relapsed or progressed. CR has been reported in other series between 6 and 12 months.[13] We found CR in 74% of the cases with a mean time of 9.5 months. A previous study reported 3 relapses at 24, 48 and 144 months.[13] Our follow-up was in average of 12 months (2-57 months), without relapses. Longer follow-up might help to better characterize the type and time of recurrence.

Considering the amount of patients seen at our Institution with IGM and the information presented in this report, we propose the following approach for evaluation and treatment of patients with IGM:

- For localized disease and mild symptoms, observation with close clinical and radiographic follow-up is warranted, considering that these lesions could resolve without intervention.[8]
- Antibiotics should be used in the presence of abscess and/or purulent drainage.
- For patients with more extensive disease and severe symptoms, including pain or sinus formation, a trial of steroids is recommended. While the patient remains symptomatic, maintenance of prednisone is recommended until resolution.[3]
- Surgical excision should only be considered in patients with treatment failure and nonresponse to more conservative treatment.

IGM is a rare, benign breast condition that may mimic inflammatory breast cancer.[14] Ultrasonography and mammography findings reveal characteristic data that can be useful for diagnosis; however, breast biopsy is the gold standard for diagnosis and should be taken in any patient even with a mild suspicion of cancer, and in all cases of relapsing mastitis.

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