GRANULOMATOUS MASTITIS: PROBLEMS OF DIAGNOSIS AND TREATMENT

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ABSTRACT

Background: Idiopathic granulomatous lobular mastitis (IGLM) is an uncommon non-specific inflammatory disease of the breast. The IGLM is a benign condition and it confuses the surgeons with cancer owing to its progressive breast lump. In the present study, the clinical characteristics, experiences of diagnosis, treatment, and outcomes of one and half year follow-up of 22 patients met the required histological criteria of idiopathic granulomatous lobular mastitis were examined and evaluated.

Subject and Methods: Between first November 2016 and 30th April 2018, twenty two married, parous, non-smoker, and non-alcoholic patients diagnosed with IGLM with an average mean of 32.5 years (23-41 years old) were included in the study. The patients underwent breast ultrasonography for the clinical features following clinical examinations. The first choice of the diagnosis was the fine needle aspiration cytology (FNAC) and the false negative results were sent to the core needle biopsy (CNB) for the final confirmation. No patients underwent mammography and breast magnetic resonance imaging. The patients have received steroids following accomplishment of antibiotics time period. The incision and drainage were performed for the patients with mass or abscesses and were followed-up for one and half year to find out the response or recurrence.

Results: The study showed that mass, skin thickening, and pain were the most prevalent clinical features and abscess as the sign in patients with IGLM and their clinical characteristics were unilateral. Only 6 patients had given history of taking oral contraceptive. The common physical findings of clinical features and ultrasonographic finding were irregular hypoechoic mass and collection (20 cases); multiple (14 cases); with an abscess (11 cases). The same numbers of patients were diagnosed with FNAC and CNB. The patients received steroids therapy, underwent drainage and excision were 13, 13, and 9, respectively. Of the total patients, the lesions of 15 patients were healed and the recurrence rate was 31.8%.

Conclusions: The patients were diagnosed with IGLM and recruited in the present study responded to different therapeutic interventions and the healing rate was 68.2%.

Keywords: Granulomatous mastitis; diagnosis; management; complications

Diagnosis of idiopathic granulomatous lobular mastitis (IGLM) is a rare non-infectious inflammatory disease of the breast. It usually developed within the mammary lobules with a necrotic pathological feature. The incidence of this disease is so low and account about 1.8% of benign breast diseases. IGLM is a benign clinical condition and a patient with the condition is presented with a firm mass faces the surgeon difficulties to distinguish it from breast cancer and...
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tuberculosis\(^3\), it may be multiple or recurrent abscesses. Sometimes, the mass is touchable and painful and overlying skin. The search for the causes of this disease continues\(^5\).

The usual clinical presentations of the patients with IGLM are hard lumps in the breast without clear systematic disease’ signs. It has some local symptoms such as pain, nipple retraction, overlying skin inflammation, discharge in nipple, fistula, and enlargement in lymph nodes. The disease mostly occurs in a unilateral direction\(^5,6\).

The disease in its clinical manifestations and radiological findings closely resembles the duct ectasia/periductal mastitis complex and tuberculosis mastitis\(^6\). The disease in its microscopic characteristics is a chronic non-necrotizing granulomatous inflammatory condition within the breast tissue lobules and histopathologically is a non-necrotizing granulomatous lobulitis with pathognomonic micro-abscesses\(^7\).

The causing factors and development of IGLM are unknown. However, it is assumed that some factors could account for the disease include autoimmune response; pregnancy; breastfeeding; oral contraceptive use; and bacterial infections\(^8\).

The management of IGLM is controversial. Antibiotics, steroid, lobular excision, drainage, and mastectomy were suggested to treat this disease in the literature. However, the optimal management plan is still not-decisive. Some surgeons recommended complete surgical excision; however, it must be kept in mind that the disease has a recurrence in some patients and repetitive surgical interventions result in poor cosmetic appearance\(^9\).

The clinical characteristics of 22 patients with idiopathic granulomatous lobular mastitis, the surgeons’ experiences of management were examined and evaluated in the present study.

PATIENTS AND METHODS

Study design and sampling

In this non-randomized clinical trial, a total of 25 married, parous, non-smoker and non-alcoholic female patients diagnosed with granulomatous mastitis were included. The patients were recruited from the outpatient clinic of surgery department of Azadi Teaching Hospital. The IGLM was diagnosed through clinical examination, radiological, and pathological findings. The ethical clearance was obtained from the Kurdistan Board for Medical Specialties (KBMS)-Erbil in 2016 and written consent form from all patients. The patients were underwent different therapeutic interventions and were followed-up for a maximum one and half year (between 3 and 18 months) for treatment outcome between 1\(^{st}\) November 2016 and 30\(^{th}\) April 2018. Of the total 25 breastfed patients, 22 of them were recruited and followed-up in the study. Three patients rejected to participate owing to pregnancy (one patient) and personal issues (two patients).

Inclusion and exclusion criteria

The patients met following eligibility criteria were included in the study:

- Chronic abscess, abscess not respond to antibiotics, multiple abscess, chronic sinus, fistula, skin swelling and
edema, inflammatory features on ultrasonography, and mass biopsy

- Confirmed their final diagnosis with granulomatous mastitis through the histopathological evaluations.

The other granulomatous lesions were excluded through the clinical examination, breast ultrasonography, and biochemical tests including:

- infections: mycobacterium tuberculosis; blastomycosis; cryptococcosis; histoplasmosis; actinomycosis; filarial infection; corynebacterium,
- autoimmune process: Wegener granulomatosis; giant cell arteritis; and foreign body reaction,
- duct ectasis: plasma cell mastitis; subareolar granuloma; and periductal mastitis, sarcoidosis; fat necrosis.
- No cases were found with breast tuberculosis\(^{10}\), therefore, anti-TB treatments were not received by any patient\(^{11,12}\).

**Treatment and Follow-Up**

Initially, the patients were screened through the physical and clinical examinations and were referred to breast ultrasonography as the first stage of diagnosis.

The patient received steroid therapy following drainage and antibiotics period accomplishment and those patients did not receive the steroid were undergone excision. Patients received a high dose of steroid (1 mg/Kg/day) for 4-8 weeks. Subsequently, the prescribed dose of steroid was lowered to 0.5 mg/Kg/day for 3-4 months. The type of antibiotics was determined following receiving sensitivity tests results from the laboratory.

The patients were followed-up monthly through the physical and clinical examination of breast for the side effects features of steroid therapy. The patients were sent to breast U/S for every 2-3 months to find a good response. Following that the complications were treated accordingly.

**Measurement and diagnostic criteria**

The results of the clinical examinations and ultrasonography whether mass, sinus, skin thickening, nipple discharge, breast discharge (non-nipple site), fever, pain, irregular hypoechoic mass and collection, being single or multiple, cellulitis, abscess, and axillary lymphadenopathy were recorded in a pre-design questionnaire.

It is difficult to obtain the detailed understanding of the IGLM through the FNAC technique and its specificity is poor\(^{6}\), but since it is a minimally invasive diagnostic technique, the surgeons decided to use it as the first diagnostic method. However, those cases not diagnosed by FNAC were sent for core needle biopsy (CNB) for the final decision as the FNAC specificity is low and accuracy of CNB is 100% in GM diagnosis\(^{8}\).

The inflammatory reactions with granulomatous was diagnosed with histopathological results consisting foamy (epitheloid) histocytes, and multinucleated (langhans) giant are accompanied by plasma cells, lymphocytes and eosinophils in centre of lobules.

The patients were not undergone mammography as it is a non-specific method and unable to give the easy findings to distinguish from breast cancer.
resulting in misdiagnosis\textsuperscript{13, 14, 9}. The breast MRI was not used as the primary diagnostic technique as it is a sensitive technique to a malignant disease\textsuperscript{15} and is efficient when ultrasound and mammography unable to take a decision\textsuperscript{16} and its specificity is not adequate (37-86\%), and it is performed for older women\textsuperscript{17}.

**STATISTICAL ANALYSIS**

The data were entered into the SPSS version 24:00 and descriptive purposes of the study were determined through the frequency distribution. The association of response with the treatment techniques was examined through the Fishers’ exact test. The $P$-value less than 0.05 was considered as a statistically significant association.

**RESULTS**

The mean age of the patients recruited in the current study was 32.50 years (Range: 23-41 year). The clinical presentations were mass in 21 cases and pain in 14 cases (Table 1). The site of disease and frequency of its occurrence were right in 11 cases and left in 9 cases (Figure 1). Only 3 cases were found to have past hypertension and, 8 of them had past surgical history such as an appendectomy. Only 6 of them had used oral contraceptive and 3 of the patients had a family history of IGLM (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Clinical Presentations and History of Patients with Idiopathic Lobular Granulomatous Mastitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>General, clinical presentations, and history (n=22)</td>
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<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Age, year</strong></td>
</tr>
<tr>
<td><strong>Last pregnancy, year</strong></td>
</tr>
<tr>
<td><strong>Clinical presentations</strong></td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Mass</td>
</tr>
<tr>
<td>Discharge</td>
</tr>
<tr>
<td>Sinus</td>
</tr>
<tr>
<td>Nipple discharge</td>
</tr>
<tr>
<td>Skin thickening</td>
</tr>
<tr>
<td><strong>Symptom duration, month</strong></td>
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<tr>
<td><strong>Side</strong></td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Left</td>
</tr>
<tr>
<td>Bilateral</td>
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<tr>
<td><strong>Time</strong></td>
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<tr>
<td>First time</td>
</tr>
<tr>
<td>Second time</td>
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<tr>
<td>More than two time</td>
</tr>
<tr>
<td><strong>Occurrence for multi-time</strong></td>
</tr>
<tr>
<td>Same place</td>
</tr>
<tr>
<td>Not same place</td>
</tr>
</tbody>
</table>

*median and Interquartile and **mean and standard deviation range were performed for statistical calculations.*

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The ultrasonography showed irregular hypoechoic mass and collection in 20 patients; 14 cases with multiple lumps; abscess in 11 cases; and axillary lymphadenopathy in 7 patients. The FNAC and biopsy tests showed that 11 patients had IGLM through the FNAC and 11 through the core needle biopsy. The tissues of cases underwent drainage were sent for pus for sensitivity culture for exclusion criteria of antibacterial sensitivity with no case with positive results and no patient underwent mammography or magnetic resonance imaging (MRI) (Table 2).

To treat the disease, all patients were undergone antibiotics for a median two weeks (empirical therapy); 13 of them were prescribed with steroid for a median 6 months. Drainage and excision were performed for 13 and 9 patients, respectively. Finally, 15 patients had a good response (68.2%) and remaining 7 patients were presented with a recurrence disease (31.8%). The only complication was seen following steroid therapy was epigastric pain in 4 patients, as shown in Table 2.

The study did not show that good response is associated with steroid therapy (P=0.397) and surgical therapy (excision) (P=0.376), as shown in Table 3.

Figure 1: Frequency Distribution of the Mass Sites

![Figure 1: Frequency Distribution of the Mass Sites](image)

Table 3: Association of Response with Management Methods in IGLM Patient

<table>
<thead>
<tr>
<th>Treatment methods</th>
<th>Good response</th>
<th>Recurrence</th>
<th>P-value (two-sided)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td>10 (66.7%)</td>
<td>3 (42.9%)</td>
<td>0.376</td>
</tr>
<tr>
<td>Surgery**</td>
<td>5 (33.3%)</td>
<td>4 (57.1%)</td>
<td>0.376</td>
</tr>
</tbody>
</table>

*Fishers' exact test was performed for statistical analyses. **Surgery includes excision, quadrantectomy, mastectomy
Table 2: Diagnostic Methods, Management intervention, and Follow-up

<table>
<thead>
<tr>
<th>Diagnosis and management</th>
<th>Frequency Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
</tr>
<tr>
<td>Irregular hypoechoic mass and collection</td>
<td>20</td>
</tr>
<tr>
<td>Lump</td>
<td>36.4</td>
</tr>
<tr>
<td>Single</td>
<td>14</td>
</tr>
<tr>
<td>Multiple</td>
<td>5</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>8</td>
</tr>
<tr>
<td>Abscess</td>
<td>11</td>
</tr>
<tr>
<td>Axillary Lymphadenopathy</td>
<td>7</td>
</tr>
<tr>
<td>FNAC findings, GM</td>
<td>11</td>
</tr>
<tr>
<td>Core needle biopsy</td>
<td>11</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>22</td>
</tr>
<tr>
<td>Antibiotics duration, week*</td>
<td>2.0</td>
</tr>
<tr>
<td>Steroid</td>
<td>13</td>
</tr>
<tr>
<td>Steroid duration, month*</td>
<td>6.0</td>
</tr>
<tr>
<td>Surgery</td>
<td>13</td>
</tr>
<tr>
<td>Drainage</td>
<td>9</td>
</tr>
<tr>
<td>Excision</td>
<td>1</td>
</tr>
<tr>
<td>Mastectomy**</td>
<td>4</td>
</tr>
<tr>
<td>Follow-up</td>
<td>15</td>
</tr>
<tr>
<td>Good response</td>
<td>7</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4</td>
</tr>
</tbody>
</table>

*Median and interquartile range was performed for statistical calculation. **This case has been underwent excision before mastectomy.

DISCUSSION

The present study showed that the mass, pain, and skin thickening were the most prevalent clinical presentations to the clinic. The patients were diagnosed with different medical techniques, whether ultrasonography, FNAC, CNB, or clinical examinations. Moreover, the treatment of choice for the disease was not uniform for all patients. The patients were received antibiotics, steroids, and some surgical procedures. The most important finding of the study was a good response in 15 patients and a recurrence result in 7 cases. The usefulness and reliability of FNAC for mass diagnosis is debatable, however, we used it as the first diagnostic tool because it is minimally invasive technique and wide available. The patients were diagnosed with FNAC as normal interpretations were sent to CNB for the final decision. However, the same numbers of patients were diagnosed with FNAC and CNB (11 cases in each method). The reason behind sending the normal result by FNAC to the CNB backs to its low specificity.

The breasts masses were hard, not smooth, and poorly mobile reflecting a change in its place following the second and more visiting of the patients to the clinic. These kinds of the features are repeatedly reported in the literature.

Of those 13 patients underwent the steroid and followed-up, 9 of them got good response. Nine of the cases were managed by excision and one of these 9 cases was managed by mastectomy and one by quadrantectomy following recurrence.

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Some investigators recommend the surgical techniques such as incision, drainage, extensive lumpectomy, quadrantectomy, ipsilateral mastectomy as the first therapeutic plan for IGLM management\textsuperscript{21}. Abscess incision and drainage may not completely remove the lesion area, subsequently, the wound may not be easily recovered leading to fistula, and hence the surgery may be the only appropriate treatment technique for patients with large abscesses for facilitation of secondary surgical resection. It may be the extensive lumpectomy and quadrantectomy are appropriate techniques for these kinds of patients as IGLM is a benign disease and mastectomy is not an acceptable way for the majority of patients. However, the medical texts suggest that the mass excision must be avoided to prevent persistent wound discharge and failure to heal in patients with a breast mass\textsuperscript{3}. Anyhow, the condition is required to be diagnosed and observed without specific treatment as it usually resolves gradually and slowly between 6 and 12 months. Those abscesses need fine needle aspiration or mini-incision and drainage have a strong tendency for recurrence\textsuperscript{22}. The authors unable to present any reason behind the high rate of recurrence (31.8\%) in the present study, but it may be the main reason as the incision and drainage were performed for approximately half of the patients.

The first step of the therapeutic plan by the surgeons in the present study was steroids following accomplishment of antibiotics time period. The literature recommends the antibiotics before and after surgery, therefore, if they received the antibiotics prescription from the general practitioners did not make an interruption in our therapeutic plan. Corticosteroids have been reported to be beneficial for IGLM treatment and may effective to avoid the disability of surgical procedures. It is recommended a short high-dose of steroids in patients with recurrence following biopsy or delayed wound healing\textsuperscript{19}. But, the surgeons must consider the adverse side-effects of steroids as they may lead to variable efficacy and recurrence on therapy cessation. Subsequently, immunosuppressive drugs such as (methotrexate and azathioprine) are used alternatively as steroid sparing agents in an immunomodulatory dose to maintain remission and prevent serious complications of steroid\textsuperscript{23}.

Since the recurrence, secondary infection, and fistula formation are well-known complications of IGLM, therefore, a long-term follow-up for these patients is suggested. Although treatments with steroids are lengthy and lasts close to 6 months, the literature has confirmed their good response\textsuperscript{13, 24, 25}. It has been reported that methotrexate or in combination with other steroids had a good response\textsuperscript{26, 27}. The good results have been obtained following a combination therapy of corticosteroids and prolactin lowering medicines like bromocriptine or cabergoline\textsuperscript{14, 18, 28}.

The rate of recurrence following therapy is between 5\% and 50\%\textsuperscript{4, 29}. Aghajanzadeh et al\textsuperscript{18} reported the 5\% of recurrence rate in IGLM management with different therapeutic methods. The patients recruited in the present study were all married, breastfed, non-smoker, and non-alcoholic, therefore, we unable to make a link with
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these factors for recurrence. However, it must be mentioned that recurrence as the result of steroid and surgery is comparable, 42.9% versus 57.1%, respectively. Usually the patients do not need further therapy following surgery but common outcomes of treatment such as recurrence, infection, sinus information, and delay healing of wound preclude the surgeon to stop the treatment. Ergin et al.\textsuperscript{30} reported a 40-year old case who did not respond to the steroid therapy following several months and showed the recurrence after two years of bilateral mastectomy. The patient had not any risk factors for granulomatous mastitis. No any reason for this recurrence was mentioned and it is frequently reported in the literature\textsuperscript{13, 31} except the possible important role of a high level of prolactin\textsuperscript{32}. In addition, it has been reported that 50% of recurrence rate has been seen following therapy cessation\textsuperscript{33}.

IGLM in non-pregnant women associated with a high serum prolactin level has been rarely reported related to pituitary adenoma, metoclopramide-related galactorrhea with blunt trauma, and phenothiazine-induced hyperprolactinemia\textsuperscript{29}.

Prolactin has immunemodulatory impacts through interference with B cell tolerance, apoptosis inhibition, enhancement of antigen presentation, regulation of cytokine production, and increase in secretion of autoantibody. This supports this idea that prolactin may have a role in making interruption in tolerance\textsuperscript{34}.

The disease is a rare condition; hence the majority of surgeons have a limited experience in its management in clinical settings making difficulties for them to choose a suitable treatment. The findings reported in the present study must be interpreted in the illumination of study design and sample size. Since the disease is a rare condition, the authors unable to reach more than this number, also three of them rejected to partake in the study. We could not report the rate of misdiagnosis, but we believe that it is low as the final decision was made by CNB. The present study showed that mass, pain, and skin thickening were the most prevalent clinical features of the patients. The authors concluded that IGLM is a challenging medical condition, as the surgeons need to apply heterogeneity of treatments for different patients. The rate of recurrence was high in the current study. The authors recommend to the surgeons to focus on steroids as the first choice of treatment.

REFERENCES


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نوخیه

چاره‌سازیا چرک بوونا دندکین یا ممکن: نهایتی‌ای ل ناسین و دیفیران کرن

ثبت‌کننده: چرک بوونا دندکین یا نهایتی یا ممکن نخوشه‌کا ناخاله ومحمد و زور کیم. نطف نخوشه‌خ خوانن روش‌شا
تومورین سفکه، لازما نوزاد دگن زدم تومورا یک بند از تر پنج‌شهرین پیشانی و دیفران. ل فکولینا برست،
زاینری به کلینیکی، سرورین ناسین، دیفیران کرن، و نخجامت نیک و نیف سالی ز ۲۲ نخوشه‌ها ورین ناسین ب
نخوشه‌خ چرک بوونا دندکین یا ممکن دهته پیشی‌کشگرین.

ریکین فلکولینی: دنیای ۲۰۱۸/۵/۲۰، ۲۲ نخوشه خیزاندار، خودان زاروک، نیکچی‌گیری‌ت، نه عمق
فهخرلار هرتن ناسین ب چرک بوونا دندکین یا نهایتی ب نظاهه ان تمینی ۳۲ سال (۳۲ سالی ۴ سالی) ل فکولینی هرتن
خوانن. نخوشه پشتی فرهنگین کلینیکی لازم سونه‌رین هرتن ناسین ب ناسینا سالوختن کلینیکی ناسینا داویا نخوشه‌ی
پشتی هراتن ب یاپوسیا دم‌ری هور مسیر به‌جانی باپوسیا دم‌ری گی بو. هیچ نخوشه‌کا لازم مامگراماف و رئینین
نههتن دانن. پشتی خلان بو دانی‌نتی باپوسیکان، نخوشه‌ان سترود و ورگرت. شق کرن و کلیش و نخوشه‌ی
خودان پچ و گرک هرتن نخجات دان دووپجو دیه دشیبین بان فلیپریک و رکاردی نیک سال و نیفان هات کرن.

نخجات: فلکولینی نیشان داشی گرک، سنور بوونا بیست، و زانی به‌لباندرین سالوختن کلینیکی نین نخوشه‌ه.
سالوختن نیک ل. چ راست نینگی پیچ نالي بو. ب تنی ۶ نخوشه حومی دژ رودیگیار و ورگرت. سالوختن
بی‌خاب‌لأتفین سونه‌رین گرکنی کریک و نیک و پوک (۲۰ نخوشه)؛ چسن گرکن (۱۴ نخوشه)؛ پیک ۱۲ نخوشه
نوخوش. زمارما و پک نیک ب باپوسیا دم‌ری هور و دم‌ری گر هرتن ناسین. نخوشه سترود و ورگرت،
مهمک هات شق کرن و ناف کلیش بزی ل ۱۲، و ۹ نخوشه‌ی هرتن نخجات دان. ز ۲۲ نخوشه‌ه، ۱۵ ز وانان
ساح بو و نخوشه‌ی ۷ کمان (۳۲٪) فلیپریک. زانی گهه د ب تنی نالوزی بین دیفیران کرنی بو.

دیفیرانجات: تپکنیکی چوداچوپانی ناسین و دیفیران کراتنی ل نخجات نوش بوونی ب چرک بوونا دندکین یا ممکن
هان بکارنین. ریزه‌ی ساخ بوونی ۲۸.۲٪ بو.
الخالصة

التهاب الضرع (الثدي) الحبيبي: مشاكل في التشخيص و العلاج

الخلفية والأهداف: تعتبر التهاب الثدي الحبيبي غير معروف السبب وباء التهابي غير مميز للثدي و نادر الحدوث. تعتبر الحالة حميدة ولكن يربك الجراح لاشتباه الحالة مع سرطان الثدي. في الدراسة الحالية تم دراسة و تقييم السمات السريرية، خبرة التشخيص والعلاج و المتابعة على مدار سنة ونصف السنة ل 22 حالة مرضية تلاقى السمات النسيجية لالتهاب الثدي الحبيبي.

طرق البحث: بين فترة تشرين الثاني 2016- نيسان 2018 تم إدخال 22 حالة مصابة بالمرض. جميعهن متزوجات، متعددات الولادات، غير مدخنات، غير ممنوع من الكحول. متوسط معدل العمر 32.5 سنة (23-41) سنة. تم إدخالهم ضمن الدراسة الحالية حيث تم إجراء فحص الثدي بالسونار بعد إكمال الفحص السريري. اختباري الأولي كانت عن طريق الفحص البدني والخزع الدقيق. في حال إعطى نتيجة سلبية ضعيفة خاطئة أرسلت الحالات إلى الخزع النسيجي اللازم لتأكيد التشخيص النهائي. تم وضع الحالات على العلاج بالستيرويد، وفتح الخراج، وتشخيص الإصلاح في الحالات. تم اكمال العلاج بالستيرويد، وفتح الخراج، استئصال العقد في 13 حالة، 9 حالة على التوالي. النتائج: الحالات التي تم تشخيص بمرض التهاب الثدي الحبيبي و التي ادخل في الدراسة. استجبن لتنوع مختلفة من التدخلات العلاجية مع نسبة شفاء 68.2%.

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