

The Role of Corynebacterium in The Etiology of Granulomatous Mastitis

 Gizem Yaman¹,  Sadullah Girgin¹,  Nezahat Akpolat¹,
 Nurullah Uzuner¹,  Eda Yıldızhan

¹ Department of General Surgery, Tatvan State Hospital, Bitlis, Adana, Türkiye

² Department of General Surgery, Faculty of Medicine, Dicle University, Diyarbakır, Diyarbakır, Türkiye

³ Department of Microbiology, Faculty of Medicine, Dicle University, Diyarbakır, Türkiye

⁴ Department of Histology and Embryology, Faculty of Medicine, Dicle University, Diyarbakır, Türkiye

Abstract

Aim: Granulomatous mastitis (GM) is a rare, benign, chronic inflammatory illness of the breast. It is characterized by necrotizing granulomatous lobulitis of the breast that clinically mimics breast cancer. In this study, we aimed to examine the existence of Corynebacterium strains thought to be covered in the etiology of idiopathic granulomatous mastitis.

Methods: We retrospectively analyzed the results of 201 breast tru-cut biopsies carried out for diagnostic purposes in the Department of General Surgery. The tissue samples of 41 patients with histopathologically diagnosed GM were examined by Gram staining. The existence of Corynebacterium kinds was investigated microscopically by adding appropriate medium.

Results: The mean age of 41 female patients with GM was 35.7 years and the age range was 20-58 years. Corynebacterium amycolatum was defined as the causative microorganism after microbiologic examination of the tissue sample of only one patient (2.4%).

Conclusions: We consider that Corynebacterium is not the etiologic agent of GM. Additionally studies with large case series are needed to explain the etiology.

Keywords: Mastitis, Corynebacterium, Granulomatous mastitis.

1. Introduction

Granulomatous mastitis (GM) is a rare chronic inflammatory illness of the breast first defined by Kessler and Wolloch in 1972¹. It is characterized by necrotizing granulomatous lobulitis of the breast that clinically mimics breast cancer. Kessler and Wolloch thought that the local immune response against secretions extravasated from the lobules played a role in the pathogenesis because most patients diagnosed with GM were in the lactation period at the onset of symptoms or had given birth before². Infectious agents such as tuberculosis, histoplasmosis, corynebacterium, and Wegener's granulomatosis, sarcoidosis and diabetes mellitus (DM) have been recommended to play a role in the etiology³.

Microbiologic diagnosis of corynebacterium lipophilic kinds, which are considered to play a role in the etiology of GM, is difficult due to their long incubation period and difficult isolation from breast tissue samples. Since most antimicrobial agents are hydrophilic, the treatment of GM caused by corynebacterium is difficult, and these patients usually undergo multiple surgical procedures and have a history of repeated antibiotic use over months to years⁴.

The aim of this study was to determine the kinds of microorganisms isolated from GM patients, to examine the effectiveness of antibiotic therapy on infection control, and to investigate whether surgical intervention was required.

2. Materials and methods

This study was confirmed by Dicle University Ethics Committee (07/01/2021-158). In this research, the consequence of 201 breast tru-cut biopsy materials analyzed in order to diagnostic aims in the outpatient clinic of the Department of General Surgery between December 2018 and September 2020 were retrospectively analyzed. The records of 41 patients with histopathologically diagnosed granulomatous mastitis whose contact data were obtained were resolved in detail.

* Corresponding Author: Eda Yıldızhan

e-mail: edayildizhan21@gmail.com

Received: 13.09.2023, Accepted: 29.10.2023, Available Online Date: 31.12.2023

Cite this article as: Yaman G, Girgin S, Akpolat N, et al. The Role of Corynebacterium in The Etiology of Granulomatous Mastitis. J Cukurova Anesth Surg. 2023; 6(3): 449-52.

doi: 10.36516/jocass.1371406

Copyright © 2023 This is an open access article distributed under the terms of the Creative Commons Attribution-Non-Commercial-No Derivatives License 4.0 (CC-BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.



Clinical findings such as mean age, age range, place of residence (urban/rural), symptoms, duration of symptoms, affected breast, total breastfeeding duration, number of live births, breastfeeding history, pregnancy and lactation status at presentation, story of trauma, oral contraceptive use (OCS), smoking and alcohol use, comorbidities (hypertension, diabetes mellitus, cerebrovascular disease), and treatment modality were investigated. In addition, tuberculosis vaccination, previous story of tuberculosis, family story of tuberculosis and ultrasonographic findings were evaluated in detail.

Examination of Breast Tissue Samples in Microbiology Laboratory

No new investigational biopsies were taken from any patient for the study. The tru-cut biopsy tissue samples were sent to the microbiology laboratory in anaerobic transport container. The tissue pieces were placed in a sterile mortar and first dissected with a sterile scalpel. The sample was then crushed by adding approximately 1 ml of liquid medium. Homogenized samples were processed for aerobic and anaerobic culture. Sections prepared from the specimens were examined by Gram staining. In the microscopic examination, the staining characteristics of the microorganisms present, their shape and the number of microorganisms present, the presence and density of leukocytes were noted. Antibiotic susceptibility tests were performed for *Corynebacterium* species that were predominantly grown in pure culture with numerous leukocytes and bacteria in the microscope image.

Disk diffusion method was used for antibiogram. Antibiogram conclusions were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations for the year in which the strain was isolated.

3. Results

Demographic characteristics and clinical findings of 41 patients who were retrospectively analyzed in our study are summarized in Table 1. It was observed that the average time between the onset of the patients' complaints and their presentation to the hospital was 65.3 days. The birth rates of the patients and the percentage of the number of children they had are shown in Table 2. All patients who gave birth had a history of breastfeeding and all reported breastfeeding from both breasts for the same duration. No patient was pregnant or lactating at the time of admission to the hospital.

Two of the patients (4.9%) stated that they had received trauma to the diseased breast in the past. Oral contraceptive use was present in 9 patients, while 16 patients (39%) had a story of smoking. None of the patients had a story of alcohol use. The treatment received by 22 of the patients for the symptoms of the disease is shown in detail in Table 2. It was also detected that all patients had received tuberculosis vaccine (BCG) according to the national vaccination program, 1 patient (2.4%) had a story of previous tuberculosis and 3 patients (7.3%) had a family story of tuberculosis.

Ultrasonographic findings showed that the most common finding was abscess (48.8%) followed by irregular hypoechoic lesion with multiple tubular extensions (41.4%). Other findings included edema and thickening of the skin (36.6%), fistulization of the skin (29.3%), benign lymphadenopathy in the axilla on the same side (14.6%), ductal dilatation (14.6%), and heterogeneous fatty tissue with increased echogenicity (9.7%). The size of the lesions measured on USG ranged from 5 mm to 4.5 cm.

Tru-cut biopsy specimens of all patients were processed in the microbiology laboratory for aerobic and anaerobic culture by adding appropriate media. Microbiologic investigation of the tissue sample of one patient (2.4%) identified *Corynebacterium amycolatum* as the causative microorganism. The disk diffusion test for *Corynebacterium amycolatum* showed that this patient was

resistant to Penicillin G, Ciprofloxacin and Rifampicin.

Cefuroxime 500 mg 2x1 orally for 14 days was administered to 38 patients who presented with signs of inflammation in the breast. Surgical drainage was performed in 2 patients with abscess, 1 patient did not receive any treatment. Following the pathology results as idiopathic granulomatous mastitis, 1 patient (2.4%) underwent mass excision, 35 patients (85.4%) were started on steroid treatment, 1 patient (2.4%) with *Corynebacterium amycolatum* growth in tissue samples was treated with moxifloxacin 400 mg/day 1x1, and 4 patients (9.8%) did not receive any additional treatment. After 14 days of antibiotic treatment, 2 of 4 patients (4.9%) who were not given additional treatment developed recurrence during follow-up. One of the patients developed recurrence 5 months after response to the first treatment and the other patient developed recurrence 4 months later. Two patients with recurrence were also treated with steroids.

Table 1

Demographic characteristics and clinical findings of the patients

Total number of patients	41
Mean age of the patients	35.7
Age range	20-58 years
Age distribution	(40+) 29.3 % (40-) 70.7 %
Patients' place of residence	Urban 73.2 % Rural 26.8 %
Symptoms	Rash 73.1 % Swelling 60.9 % Pain 48.7 % Discharge 41.4 %
Site of involvement in the breast	Right Breast 43.9 % Left Breast 56.1 % Bilateral 0%

Table 2

Birth rates, number of children (%), comorbidities and treatment status of the patients.

Birth rates	Never given birth before (17.1 %) Gave birth before (82.9 %)
Number of births	1 birth: 8 patients 2 births: 7 patients 3 births: 11 patients 4 births: 6 patients 5 births: 2 patients
Comorbidities	Hypertension: 5 patients Diabetes mellitus: 4patients Cerebrovascular disease: 1 patient Antibiotics: 13 patients
Treatment Modality	Antibiotics+corticosteroids: 6 patients Antibiotics + corticosteroids + surgical excision: 1 patient No treatment: 2 patients

4. Discussion

Idiopathic granulomatous mastitis (IGM) is a benign inflammatory disease of the breast whose etiology is not fully understood, whose true incidence is unknown and which may clinically mimic breast cancer⁵. Some authors consider autoimmunity, infection, trauma, trauma, OCS use, ethnicity and lactation in the etiology. The fact that women diagnosed with IGM are frequently under 50 years of age and are diagnosed within 5 years of their last pregnancy suggests that childbirth and breastfeeding are involved in its etiology.

In the study by Al-Khaffaf et al. the mean age of 18 patients diagnosed with IGM was 36 years and more than half of them had a story of delivery within 5 years⁶. Shin et al. reported in their study that the mean age of 34 patients diagnosed with IGM was 37 years, 32 of these patients were in reproductive age, and the mean duration from the last birth to the time of diagnosis was 38 months⁷. Bani-Hani et al. reported that the mean age of 24 patients diagnosed with IGM was 34.3 years and 4 of 22 patients with a story of delivery had active pregnancy at the time of diagnosis⁸. In our study, the mean age of the patients was 35.7 years, 34 patients (82.9%) had a story of delivery and 7 patients (17.1%) were nulliparous. All patients with a story of delivery had a story of lactation. None of the patients were pregnant or lactating at the time of diagnosis.

The fact that most of the patients diagnosed with IGM had a story of childbirth and lactation does not make it possible to explain the etiology only with pregnancy and lactation, considering that the disease is observed in a wide range of ages including 11-83 years⁸. Although it has been reported in the literature that some patients diagnosed with IGM used OCS, no relation was found between OCS use and IGM⁵. In the study by Shin et al. 5 out of 34 patients (14.7%) used OCS⁷, in the study by Barreto et al. 15 out of 90 patients (17.2%) (73), and in the study by Girgin et al. 9 out of 49 patients (18.4%) had a story of OCS use (9). In our study, 9 patients (21.9%) had a story of OCS use.

In studies, smoking has been considered to be a factor in the etiology of IGM. It was reported that 8 of 49 patients (16.3%) in Girgin et al.'s study⁹, 4 of 8 patients (50%) in Özel et al.'s study¹⁰, and 7 of 75 patients (9.33%) in Jieqing Li's study¹¹ had a story of smoking. In our study, 16 of 41 patients (39%) had a story of smoking.

Autoimmunity, local trauma, sarcoidosis, diabetes mellitus have been observed as triggering factors in the etiology of IGM. Girgin et al. 49 patients did not report a story of local trauma, DM, autoimmune disease⁹. In a study conducted by Özşen et al. on 90 patients, it was reported that sarcoidosis was diagnosed in 1 patient¹². In our study, 4 patients had a story of DM and 2 patients had a story of local trauma to the diseased breast in the past.

Tuberculous mastitis is a rare clinical entity that frequently affects African and Indian women. It may be a part of systemic tuberculosis or may present as isolated mastitis. Agarwal et al. reported that tuberculosis was responsible for the etiology in 4 out of 10 patients diagnosed with GM¹³. Tuberculosis was found in 9 out of 34 patients in the study by Shin et al.⁷, 1 out of 90 patients in the study by Özşen et al.¹², 27 out of 33 patients in the study by Chandanwale et al.¹⁴, and tuberculosis was not detected in any patient in the studies by Prasad et al.¹⁵, which included 73 patients, and Girgin et al.⁹, which included 49 patients. In our study, 1 patient (2.4%) had a history of previous tuberculosis. In our study, PPD test after histopathologic diagnosis and ARB results in sputum for 3 consecutive days were negative in all patients.

A review of the literature reveals that large case series of GM have been reported from the Middle East, Mediterranean countries, Asia and the Americas. The high prevalence of GM among women of Asian, Hispanic and Arab origin has led to a debate about ethnicity¹⁶. In the study published by Al-Khaffaf et al. in 2008, it was reported that 10 (56%) of 18 patients diagnosed with IGM were Caucasian, 5 (28%) were Asian, 2 (11%) were Afro-Caribbean and 1 (5.5%) was of Central Asian origin⁶. In a study conducted by Gautier et al. in 2013, it was reported that 5 of 11 patients were of Canadian, 2 of Latin American, 2 of Arab and 1 of Russian origin⁵. In our study, all patients lived in the Southeastern Anatolia Region, 30 patients (73.2%) lived in urban areas and 11 patients (26.8%) lived in rural areas.

The normal endogenous bacterial flora of the breast is similar to

that of the skin. Coagulase-negative Streptococci, Propionibacterium species and Corynebacterium species are the dominant microorganisms¹⁷. Since Corynebacterium species are a member of the normal skin flora, their isolation in cultures of breast tissue samples of patients diagnosed with GM is considered contamination¹⁸. Taylor et al. reported a striking association between GM and Corynebacterium. In a study of 34 patients with GM, he described a histologic type that included granulomatous and neutrophilic inflammation surrounding a central lipid/cystic area. Gram positive bacilli were detected in these cystic cavities. It was reported that Corynebacterium species were isolated from 52 of 116 tissue samples obtained from these 34 patients with an average of 3.44 tissue samples. When compared with the control group, a significant difference was found¹⁹.

Funke et al. in their study in 1997, argued that in order to associate Corynebacterium species with a disease, Corynebacterium should be observed in a tissue sample taken under sterile conditions. They also suggested that polymorphonuclear leukocyte reaction and gram-positive bacilli should be present to consider infection due to Corynebacterium²⁰.

In the study of Dobinson et al., *C. kroppenstedtii* was isolated most frequently with 10 patients and *C. tuberculoearicum* was isolated second frequently with 4 patients⁴. In a study conducted by Shoyele et al. on 7 patients, *C. amycolatum* was isolated in the tissue sample of one patient¹⁸. In the study by Troxell et al. Corynebacterium was isolated in 3 of 35 patients with a diagnosis of GM²¹. In the study by Taylor et al. *C. kroppenstedtii* was isolated in 13, *C. tuberculoearicum* in 10 and *C. amycolatum* in 2 of 28 patients diagnosed with GM¹⁹. Kivılcım et al. reported that no bacterial DNA belonging to any normal skin flora including Corynebacterium was detected in tissue samples in a study conducted on 51 patients²⁰.

Paviour et al. reported that Corynebacterium was isolated in 24 patients and *C. kroppenstedtii*, *C. tuberculoearicum* and *C. amycolatum* strains were isolated in 13, 3 and 3 of these patients, respectively. They stated that most of the patients received antibiotherapy with more than one surgical procedure. In this study, 1 patient in whom both *C. kroppenstedtii* and *C. amycolatum* were isolated from tissue samples was treated with intravenous penicillin for 3 weeks. Subsequently, doxycycline 100mg orally with high fat solubility was administered as there was no response to treatment. After doxycycline treatment, surgical intervention was not needed in this patient²².

In a case report of breast abscess with fistula formation, Butta et al. performed abscess drainage and fistula excision, continued the treatment with amoxicillin+clavulanic acid 1000mg (875/125mg) and doxycycline 200 mg for 7 days upon isolation of *C. amycolatum* in the tissue sample and reported that the patient responded fully to the treatment and recovered completely²³.

In our study to investigate the role of Corynebacterium strains in the etiology of granulomatous mastitis, tissue samples obtained from 41 patients were examined microscopically in terms of the number of microorganisms, staining characteristics and shapes of the existing microorganisms, and *C. amycolatum* was isolated from only 1 patient (2.4%). According to the disk diffusion test result for antibiotic, moxifloxacin 400mg/day treatment was given to this patient and a successful treatment was provided. After initial cefuroxime treatment, 2 of 4 patients who were not given any other treatment had recurrence and were treated with steroids. When the last treatment in which the patients in our study showed improvement is analyzed; cure was achieved with steroid treatment in 90.3% of the patients.

In our study, we investigated tissue culture samples for many microorganisms, especially Corynebacterium strains. At the end of the study, we observed that *C. amycolatum* was isolated from the tissue

samples of only one patient and most of the patients were cured with steroid treatment.

5. Conclusions

Corynebacterium, which has been considered as a contamination in the past, but is thought to be the causative agent of granulomatous mastitis etiology by various studies, was isolated from the tissue culture of only one of the 41 patients in our study. Failure to demonstrate the presence of Corynebacterium in the studies performed with molecular methods has led us away from the thesis that Corynebacterium is the causative agent in the etiology of GM. The etiology of idiopathic granulomatous mastitis is still unclear and further studies with large case series are needed.

Statement of ethics

The study was approved by the Ethics Committee of Dicle University Ethics Committee (07/01/2021-158)

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

References

- Erhan Y, Veral A, Kara E, et al. A clinicopathologic study of a rare clinical entity mimicking breast carcinoma: idiopathic granulomatous mastitis. *The Breast*. 2000; 9(1): 52-6.
<https://doi.org/10.1054/brst.1999.0072>
- Imoto S, Kitaya T, Kodama T, et al. Idiopathic Granulomatous Mastitis: Case Report and Review of the Literature, *Japanese Journal of Clinical Oncology*. 1997; 27(4): 274-7.
<https://doi.org/10.1093/jjco/27.4.274>
- Schelfout K, Tjalma WA, Cooremans ID, et al. Observations of an idiopathic granulomatous mastitis. *Eur J Obstet Gynecol Reprod Biol*. 2001; 97(2): 260-7.
[https://doi.org/10.1016/s0301-2115\(00\)00546](https://doi.org/10.1016/s0301-2115(00)00546)
- Dobinson HC, Anderson TP, Chambers ST, et al. Antimicrobial Treatment Options for Granulomatous Mastitis Caused by Corynebacterium Species. *J Clin Microbiol*. 2015; 53(9): 2895-9.
<https://doi.org/10.1128/JCM.00760-15>
- Gautier N, Lanolde L, Tran-Tranh D, et al. Chronic Granulomatous Mastitis: Imaging, Pathology and Management, *European Journal of Radiology*. 2013; 82 (4): e165-75.
<https://doi.org/10.1016/j.ejrad.2012.11.010>
- Al-Khaffaf B, Knox F, Bundred, NJ. Idiopathic granulomatous mastitis: a 25-year experience. *J Am Coll Surg*. 2008; 206(2): 269-73.
<https://doi.org/10.1016/j.jamcollsurg.2007.07.041>
- Shin YD, Park SS, Song YJ, et al. Is surgical excision necessary for the treatment of Granulomatous lobular mastitis? *BMC Womens Health*. 2017; 17 (1): 49.
<https://doi.org/10.1186/s12905-017-0412-0>
- Bani-Hani KE, Yaghan RJ, Matalaka II, et al. Idiopathic granulomatous mastitis: Time to avoid unnecessary mastectomies. *Breast J*. 2004; 10 (4): 318-22.
<https://doi.org/10.1111/j.1075-122X.2004.21336.x>
- Girgin S, Uslukaya O, Yilmaz E, et al. Granulomatous mastitis: A retrospective review of 49 patients. *Dicle Medical Journal*. 2015; 42(1): 22-7.
<https://doi.org/10.5798/diclemedj.0921.2015.01.0524>
- Ozel L, Unal A, Unal E, et al. Granulomatous mastitis: is it an autoimmune disease? Diagnostic and therapeutic dilemmas. *Surg Today*. 2012; 42(8): 729-33.
<https://doi.org/10.1007/s00595-011-0046-z>
- Li J. Diagnosis and Treatment of 75 Patients with Idiopathic Lobular Granulomatous Mastitis. *J Invest Surg*. 2019; 32(5): 414-20.
<https://doi.org/10.1080/08941939.2018.1424270>
- Ozgen M, Tolunay S, Gokgoz MS. Granulomatous Lobular Mastitis: Clinicopathologic Presentation of 90 Cases. Recurrence in Uterine Tumors with Ovarian Sex-Cord Tumor Resemblance: A Case Report and Systematic Review. *Türk Patoloji Derg*. 2018; 34(3): 215-9.
<https://doi.org/10.5146/tipath.2018.01431>
- Agarwal C, Singh K, Pujani M, et al. Are all Granulomatous Mastitis Cases Tuberculous?: A Study on the Role of Cytology in Evaluation of Granulomatous Mastitis. Are all Granulomatous Mastitis Cases Tuberculous?: A Study on the Role of Cytology in Evaluation of Granulomatous Mastitis. *Türk Patoloji Derg*. 2019; 35(2): 128-33.
<https://doi.org/10.5146/tipath.2018.01442>
- Chandanwale S, Naragude P, Shetty A, et al. Cytomorphological Spectrum of Granulomatous Mastitis: A Study of 33 Cases. *Eur J Breast Health*. 2020; 16(2): 146-51.
<https://doi.org/10.5152/ejbh.2020.5185>
- Prasad S, Jaiprakash P, Dave A, et al. Idiopathic granulomatous mastitis: an institutional experience. *Turk J Surg*. 2017; 33(2): 100-3.
<https://doi.org/10.5152/turkisurg.2017.3439>
- Wolftrum A, Kümmel S, Theuerkauf I, et al. Granulomatous Mastitis: A Therapeutic and Diagnostic Challenge. *Breast Care (Basel)*. 2018; 13(6): 413-8.
<https://doi.org/10.1159/000495146>
- Shoyele O, Vidhun R, Dodge J, et al. Cystic neutrophilic granulomatous mastitis: A clinicopathologic study of a distinct entity with supporting evidence of a role for Corynebacterium-targeted therapy. *Ann Diagn Pathol*. 2018; 37: 51-6.
<https://doi.org/10.1016/j.anndiagpath.2018.08.005>
- Taylor GB, Paviour SD, Musaad S, et al. A clinicopathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis. *Pathology*. 2003; 35(2): 109-9.
<https://linkinghub.elsevier.com/retrieve/pii/S0959646003000927>
- Renshaw AA, Derhagopian RP, Gould EW. Cystic neutrophilic granulomatous mastitis: an underappreciated pattern strongly associated with gram-positive bacilli. *Am J Clin Pathol*. 2011; 136(3): 424-7.
<https://doi.org/10.1309/AICP1W9JBRYOQSNZ>
- Kivilm T, Altintoprak F, Memiş B, et al. Role of Bacteriological Agents in Idiopathic Granulomatous Mastitis: Real or Not? *Eur J Breast Health*. 2018; 15(1): 32-6.
<https://doi.org/10.5152/ejbh.2018.4249>
- Taylor GB, Paviour SD, Musaad S, et al. A clinicopathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis. *Pathology*. 2003; 35(2): 109-9.
<https://linkinghub.elsevier.com/retrieve/pii/S0959646003000927>
- Paviour S, Musaad S, Roberts S, et al. Corynebacterium species isolated from patients with mastitis. *Clin Infect Dis*. 2002; 35(11): 1434-40.
<https://doi.org/10.1086/344463>
- Butta H, Pasha F, Dawar R, et al. Corynebacterium Amycolatum Causing Breast Abscess: An Infecting Diphtheroid with a difference. *Annals of Pathology and Laboratory Medicine*. 2017; 4: 128-30.
<https://doi.org/10.21276/APALM.1456>