Study on The Frequency of Antibiotic Use Before Diagnosis in Granulomatous Mastitis

Granülomatöz Mastitte Tanı Öncesi Antibiyotik Kullanım Sıklığı Üzerine Bir Çalışma

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Öz

Bu retrospektif kohort çalışmasında 2015-2020 yılları arasında granülomatöz mastit tanısı almış 69 hastaya ait veriler derlenmiştir. Hastalara ait demografik veriler, tanıdan önce antibiyotik alıp almadıkları, antibiyotik kullanımının türü ve süresi, patolojik tanı ile tedavi başlangıcı arasında geçen süre, mikrobiyolojik testlerde belirli bir faktörün varlığı, tanıdan sonra tedavi türü ve iyileşme süresi kaydedildi. Ortalama yaş 34.58±7.30 yıldı. Hastaların %94.2'sinin (n=65) tanıdan önce ampirik antibiyotik aldığı bulundu. Hastaların %71'i (n=53) en az iki farklı antibiyotik almıştı. Patolojik tanıya kadar geçen ortalama süre 12.7 aydı. Genellikle granülomatöz mastit tanısı patolojik olarak konulana kadar verilen ampirik antibiyotik tedavileri tanı sürecini uzatır. Bu hastalarda gereksiz ve uzun süreli antibiyotik kullanımının önüne geçmek için tanısal testlere öncelik verilmesi daha uygun olacaktır.

Anahtar Kelimeler: Ampirik Tedavi, Antibiyotik, İdiyopatik, Granulomatöz Mastit, Tedavi Yönetimi

Abstract

This retrospective cohort study compiled data from 69 patients pathologically diagnosed with granulomatous mastitis between 2015 and 2020. Patient demographics, whether they were taking antibiotics before diagnosis, the type and duration of antibiotic use, the time elapsed between pathologic diagnosis and initiation of treatment, the presence of a specific factor in microbiologic tests, the type of treatment after diagnosis, and the recovery period were recorded. The mean age was 34.58±7.30 years. It was found that 94.2% (n=65) of patients had taken empirical antibiotics before diagnosis.Seventy-one percent of the patients (n=53) had taken at least two different antibiotics.The mean time to pathological diagnosis was 12.7 months. Empiric antibiotic treatments, often given until the diagnosis of granulomatous mastitis is made pathologically, prolong the diagnostic process. It would be more appropriate to prioritize diagnostic testing to avoid unnecessary and long-term antibiotic use in these patients.

Keywords: Empiric Treatment, Antibiotic, Idiopathic, Granulomatous Mastitis, Treatment Management

Introduction

Granulomatous mastitis is a chronic inflammatory disease of the breast. This disease is divided into idiopathic and secondary. Secondary mastitis occurs due to a specific factor (1). Both infectious and non-infectious agents are found in the secondary group. In addition to factors involved in the etiology of granuloma, such as sarcoidosis, Wegener's disease, and foreign bodies, rare pathogens such as tuberculosis, corynebacteria, bacteria, fungi, and parasites are among the causes of secondary granulomatous mastitis (2). To speak of idiopathic granulomatous mastitis, it must be confirmed that there is no other etiologic cause (3).

The etiology of idiopathic granulomatous mastitis is not yet fully understood, and its association with autoimmune diseases and some rare/difficult-to-detect infectious agents is under investigation. Since the etiologic cause has not been fully elucidated, there is no consensus on treating the disease.

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Findings in patients often mimic simple mastitis symptoms. The most common findings include painful induration, redness, discharge, and temperature elevations in the breast. As these findings primarily indicate an inflammatory process, empiric antibiotic therapy is initiated, and drainage is placed in most patients before diagnosis (4). In particular, patients with idiopathic granulomatous mastitis are treated unsuccessfully with a provisional diagnosis of bacterial breast infection.

In addition to the unnecessary use of antibiotics, long-term and different types of antibiotic treatments lead to prolongation of the process and secondary damage in patients who do not benefit from treatment (5). Although granulomatous mastitis is a benign and inflammatory breast disease, morbidity can be severe.

Empiric antibiotic therapy is commonly used for many infectious diseases, considering potential factors. However, repeated use of antibiotics without differentiation between granulomatous mastitis and simple mastitis delays the diagnosis of these patients and often complicates the process. Therefore, rapid radiologic evaluation and non-delayed breast biopsy for clinical suspicion in this patient population may minimize treatment duration with rapid diagnosis and reduce recurrence and treatment resistance. It is important to initiate antibiotic therapy when an infectious agent is detected after a microbiological examination. In this study, we aimed to determine the frequency and duration of antibiotic use before

diagnosis in patients with granulomatous mastitis. We also aimed to investigate the impact of antibiotic use on the diagnostic treatment process.

Material and Method

In this retrospective cohort study, data from 90 patients with a pathologic diagnosis of granulomatous mastitis were analyzed at two different centers between 2015 and 2020. One of the centers was a 3rd-level hospital; the other was a 3rd-level hospital, and the same physicians performed all patients' diagnostic and treatment processes. Data were obtained from medical history reports and records of the physicians who led the diagnosis and treatment process. Twenty-one patients in whom the diagnosis of granulomatous mastitis could not be confirmed pathologically, whose data were not accessible, or who did not receive the recommended treatment were excluded from the study.

Patient's demographic data, whether they had taken antibiotics before diagnosis, the type and duration of antibiotic use, the type of disease onset, the time elapsed between the pathological diagnosis and the start of treatment, the presence of a specific factor in microbiological tests, the type of treatment given after diagnosis, and the recovery time were recorded. In addition, comorbidity, history of chest trauma, smoking, body mass index, menopausal status, contraceptive use, pregnancy, and breastfeeding status were recorded.

After the clinical assessment of patients, CRP, WBC, prolactin, TFT, tissue and abscess culture results, and radiological assessment results were recorded.

Only patients with a pathologically confirmed diagnosis of granulomatous mastitis were included in the study. Patients whose pathogen could not be detected in the tests performed after diagnosis for etiologic investigation were classified as having idiopathic granulomatous mastitis. This situation was also recorded in patients with an etiologic cause of granuloma.

All patients' presence, duration, and type of antibiotic therapy before diagnosis were compared, and their impact on the diagnostic and treatment process was investigated.

Statistical Analysis

The sample size for this study was calculated using G*Power software version 3.1.9.2 (Institute of Experimental Psychology, Heinrich Heine University, Düsseldorf, Germany). Due to the lack of previous research on this topic, a preliminary study was conducted to determine the sample size. The calculation was based on the Mann-Whitney U test, which was used to evaluate the central hypothesis of this study. Specifically, the sample size was derived from the treatment durations of 10 patients who received antibiotics for 7 to 14 days and 14 patients who were treated with antibiotics for more than 14 days. With a two-tailed test, type I error of 0.05, power of 80% (1-β = 0.8), and effect size (d) of 1.056, it was determined that the study should include a minimum of 16 patients in each group, totaling at least 32 subjects.

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables were normal or not was determined by the Kolmogorov-Smirnov test. The Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±SD (standard deviation) for normal distributions, and median (Q1-Q3) for skewed distributions. Categorical data were described as number of cases (%).

Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann Whitney U test were applied for comparisons of the not normally distributed data.

Categorical variables were compared using Pearson's chi-square test or Fisher's exact test.

Univariate and multiple logistic regression analyses were performed to assess the association between recurrence and risk factors findings.

First of all it was used one variable univariate logistic/lineer regression with risk factors that are thought to be related with risk factors that has p-value<0.05 univariate variable logistic/lineer regression were included to model on multivariable logistic/lineer regression. Enter model used in multivariable logistic/lineer regression. Whether all independent variables were significant in the model was analyzed with Wald statistic on multivariable logistic regression. Whether every independent variable was significant on the model was analyzed with t statistic on multivariable lineer regression.

Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff value of the time to diagnosis associated with the risk of antibiotic treatment time.

It was accepted p-value <0.05 as significant level on all statistical analysis.

Results

Data were analyzed from 69 patients with histopathologically confirmed granulomatous mastitis between 2015 and 2020. The characteristics of all patients included in the study are listed in Table 1. The mean age was 34,58±7,30 years (range 22-59 years). All patients were women, and only two patients were diagnosed with post-menopause.

Table 1. The characteristics of all patients included in the study are listed in the table below.

	n	%
Age. $\acute{X}$ ± SD (Standart deviation)	34.58±7.30	
Size of lesion. Med(Q_1-Q_3)	35.00(30.00-50.00)	
Antibiotic treatment duration		
7-14 days	16	24.6%
>14 days	49	75.4%
Time. months. Med(Q_1-Q_3)	5.00(3.00-12.00)	
Symptoms		
Mass	35	50.7%
Drainage	2	2.9%
Fistule	7	10.1%
Pain	9	13.0%
Abscess	16	23.2%
Side		
Right	34	49.3%
Left	34	49.3%
Bilateral	1	1.4%
Localization		
Retro-areolar	18	26.5%
Upper-outer quandrant	17	25.0%
Upper-inner quadrant	19	27.9%
Lower-outer quadrant	4	5.9%
Lower-inner quadrant	5	7.4%
Whole breast	5	7.4%
Surgery		
None	0	0.0%
Biopsy	57	83.8%
Excision	10	14.7%
Mastectomy	0	0.0%
Breast-conserving	1	1.5%
Recurrence		
No	49	71.0%
Yes	20	29.0%
Antibiotic use		
No	4	5.8%
Yes	65	94.2%

Examination of lesion locations revealed they were mostly located in the upper inner quadrant and retro areolar area. The first finding in most patients was a painful mass (50.7%).

Sixty-five (94.2%) patients had received antibiotic treatment before diagnosis. Patients were grouped according to antibiotic treatments received in two groups of 7-14 days and multiple antibiotic treatments of more than 14 days. Only four patients (5.8%) had not received empiric antibiotic treatment before diagnosis. Most patients (68.8%) who received antibiotic therapy of less than 14 days received amoxicillin-clavulanic acid and ciprofloxacin, and 46.9% received antibiotic treatment longer than 14 days. It was found that 17 patients also received multiple antibiotics, such as 2nd and 3rd line cephalosporins. The recurrence rate was found to be statistically significantly higher in patients whose antibiotic intake duration was more than 14 days ($p<0.05$). The rate of amoxicillin-clavulanic acid with ciprofloxacin and 2nd and 3rd line cephalosporin use was found to be statistically significantly higher in patients whose antibiotic intake duration was more than 14 days ($p<0.05$) (Table 2). Cultures were taken from 52 patients, and specific microorganisms were grown in only 3. One of these patients grew *Staphylococcus spp*., one grew *Candida albicans*, and the other grew *E. Coli* producing extended-spectrum beta-lactamase (ESBL). The culture of the re-sampled aspirate material showed no growth in all three patients.

It was noted that 13 patients were tested with PPD (Purified Protein Derivative) and 56 with IGST (Interferon-gamma release test). While the result of the PPD test was positive in 9 patients (>15mm), the IGST test was positive in 18 patients. In addition, no patient was found to stain with ARB (Asido-resistance staining) in tissue culture, and no tuberculosis culture positivity was detected.

The mean duration of symptoms before diagnosis was 12.57 months. It was observed that this period passed with various hospitalizations and empiric antibiotic treatments.

Table 2. The comparison situation in terms of other variables according to the duration of antibiotic intake is given in the table below.

	Antibiotic treatment time				p
	7-14 days		>14 days		
	n	%	n	%	
Age. $\acute{X}$ ± SD	35.69±8.33		34.46±7.17		0.573*
Size. Med(Q_1-Q_3)	40.00(30.00-50.00)		35.00(25.00-50.00)		0.267 $^{\Phi}$
Treatment time. Med(Q_1-Q_3)	3.00(2.00-7.00)		6.00(3.00-18.00)		0.060 $^{\Phi}$
Symptoms					
Mass	6	37.5%	27	55.1%	0.162 $^{\beta}$
Drainage	2	12.5%	0	0.0%	
Fistule	2	12.5%	4	8.2%	
Pain	2	12.5%	7	14.3%	
Abscess	4	25.0%	11	22.4%	
Recurrence					
No	15	93.8%	30	61.2%	**0.014** $^{\beta}$
Yes	1	6.3%	19	38.8%	
Type of antibiotics					
Amoxicillin-clavulanate(1)	11	68.8%	9	18.4%	**0.001** $^{\beta}$
(1) + Ciprofloxacin	4	25.0%	23	46.9%	
Additional antibiotics (cephalosporins etc.)	1	6.3%	17	34.7%	
Steroids					
No	10	62.5%	32	66.7%	0.761 $^{\beta}$
Yes	6	37.5%	16	33.3%	
Anti-tuberculosis					
No	10	66.7%	42	85.7%	0.132 $^{\beta}$
Yes	5	33.3%	7	14.3%	

*Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q_1-Q_3) and categorical variables are expressed as either frequency (percentage). Student t Test *, mann whitney u Test $^{\Phi}$, Chi square Test or fisher's exact test $^{\beta}$, p=Level of Significance, p<0,05*

Steroid therapy was administered to 23 (33.8%) patients diagnosed with idiopathic granulomatous mastitis. None of the patients received immunosuppressive treatment such as methotrexate. However, patients with positive IGST and/or PPD values among those who did not accept steroid treatment or who relapsed after steroid treatment received anti-tuberculous treatment. No relapse was observed in 7 of 13 patients treated this way during the one-year follow-up period.

It was noted that recurrent seizures and relapse occurred in 20 patients during the 1-year follow-up period. Although recurrence was not associated with antibiotic use alone, it is noteworthy that the number of exacerbations and course duration increased when the process was prolonged. The diagnosis of the disease was delayed until diagnosis by using empiric antibiotics (p=0.014).

Univariate logistic regression analysis was applied to determine factors that predict recurrence in patients. It was understood that variables with a p-value below 0.05 predicted or predicted relapse. Increased duration of antibiotic intake and taking multiple types of antibiotics predicts recurrence (p=0.036 and 0.042 respectively).

Variables with a p-value <0.05 in the univariate logistic regression analysis were included in the multiple logistic regression analysis. In multiple logistic regression analysis, no variable was detected that predicted recurrence (Table 3).

Table 3. Logistic Regression Analysis Applied to Determine Factors Affecting Relapse

	Univariate Logistic Regression					Multiple Logistic Regression				
	Wald	p	OR	95% C.I.for OR		Wald	P	OR	95% C.I.for OR	
Age	1.783	0.182	0.944	0.868	1.027					
Antibiotic treatment time	4.397	**0.036**	9.500	1.158	77.908	3.419	0.064	7.494	0.886	63.36
Type of antibiotics										
Amoxicillin-clavulanate (1)	0.008	0.929	0.949	0.302	2.985					
(1) + Ciprofloxacin	3.125	0.077	0.348	0.108	1.121					
Additional antibiotics (cephalosporins etc.)	4.123	**0.042**	3.273	1.042	10.278	2.007	0.157	2.358	0.720	7.725
Steroids	0.657	0.417	0.615	0.190	1.991					
Antituberculosis treatment	2.928	0.087	0.158	0.019	1.308					

Wald: test statistics, OR: odds radio, CI: Confidence interval. hosmer-lemeshow: p>0,05. Statistically significant p-values are in bold.Variables with a p value below 0.05 were included in multiple analysis.

Univariate lineer regression analysis was applied to determine the factors affecting the time to diagnosis. It was understood that variables with a p-value below 0.05 predicted the time until diagnosis. It was observed that the use of additional antibiotics (p=0.035), other than amoxicillin clavulanate, and consequently, an extended duration of antibiotic use, increases the time until diagnosis. Variables with a p-value <0.05 in the single variable lineer regression analysis were included in the multiple variable lineer regression analysis. No variable predicting the treatment duration was identified in the multiple variable lineer regression analysis (Table 4).

Discussion

Many patients on GM present with a clinical picture accompanied by inflammatory skin lesions and chest pain. Since there is no consensus on the treatment of GM, most patients are treated with antibiotics used empirically during the diagnostic investigation phase (6). Although there is limited data on antibiotic therapy in the treatment of IGM, 7-10 days of empiric antibiotic therapy is initially recommended in patients who have developed abscesses and cellulitis (7-10).

Despite antibiotic therapy, most clinicians tend to continue antibiotic therapy with different antibiotic groups or combinations if abscesses or infectious processes do not resolve and ulcers recur. GM is, by definition, a sterile inflammatory disease, and therefore antibiotic therapy often fails (11).

Recently, attention has been drawn to Corynebacterium species as a specific pathogen in GM. As Corynebacteria are part of the normal skin flora, it can be difficult to distinguish between infection, colonization, and contamination with these organisms. When isolated as pure or dominant growth of >104 cfu/ml in abscess culture, it is important to consider Corynebacterium species as causative Corynebacterial breast infections are typically characterized by abscess formation, granulomatous inflammation, and progression to sinus/fistula formation (12). In general, the lipophilic species of Corynebacterium cause mastitis (13). Of these species, *Corynebacterium kroppenstedtii* is frequently detected. Therefore, it may play a significant role in causing this disease (14). Due to the frequent detection of this lipophilic gram-positive bacillus, there is also increasing evidence of a link between Corynebacterium infection and another clinical picture called cystic neutrophil granulomatous mastitis (CNGM), which is characterized by lipo granulomas consisting of open spaces surrounded by neutrophils and granulomatous inflammation. Indeed, GM has also been referred to as "cystic neutrophil granulomatous mastitis" by some authors (15,16).

Table 4. Univariate lineer regression analysis to determine the factors affecting the time to diagnosis.

	Univariate Lineer Regression					Multiple Lineer Regression				
	β	t	p	95.0% Confidence Interval for B		β	t	p	95.0% Confidence Interval for B	
Age	-0.033	-0.264	0.792	-0.780	0.598					
Size	-0.053	-0.435	0.665	-0.327	0.210					
Symptoms										
Mass	-0.022	-0.179	0.858	-10.407	8.692					
Abscess	-0.139	-1.146	0.256	-17.637	4.774					
Others	0.158	1.311	0.194	-3.686	17.790					
Type of antibiotics										
Amoxicillin-clavulanate (1)	-0.265	-2.183	**0.033**	-22.057	-0.976	-0.189	-1.429	0.158	-19.702	3.276
(1) + Ciprofloxacin	0.010	0.080	0.936	-9.828	10.648					
Additional antibiotics (cephalosporins etc.)	0.262	2.159	**0.035**	0.874	22.634	0.184	1.393	0.169	-3.591	20.109
Antibiotic treatment time	0.051	0.405	0.687	-9.329	14.066					

β: Standardized Coefficients, t: test statistic, CI: Confidence Interval. p=Level of Significance, p<0,05. Statistically significant p-values are in bold. VIF values were found below 10 and there was no multicollineerity problem.

Considering the role of corynebacterial infections and C. kroppenstedtii in the pathogenesis of the disease, the response to antimicrobial treatments has been studied (17). It was suggested that lipophilic antibiotics with a high volume of distribution are more likely to reach adequate concentrations in lipo granulomas. Potential antimicrobial options include doxycycline and trimethoprim-sulfamethoxazole, as well as the antibiotics clarithromycin and rifampicin, which are also useful in the treatment of other granulomatous infections, including nontuberculous mycobacteria. Other treatment options, such as oral corticosteroids and immune-modulatory therapies that can suppress the inflammatory response and subsequent development of granulomatous disease, can be found at GM. The choice of the most effective antibiotic and the treatment regimen that should be used in combination remains unclear, and the optimal duration of treatment also requires further investigation. Although short-term antibiotic treatment (5-7 days) did not appear to improve

clinical outcomes in one study, repeated short-term treatments are generally preferred (18).

Information on the use of antibiotics in the treatment of IGM is limited. Nevertheless, 7-10 days of antibiotic treatment may be recommended in cases with cellulitis, abscess, and sinus formation (19).

Granulomatous mastitis is among the most critical subgroups in patients with mastitis findings. Empiric antibiotic treatments, which are often preferred in patients who are not lactating and are known to have recurrent episodes of mastitis, lead to a delay in diagnosis.

It is important to prioritize investigations in the differential diagnosis to identify the etiology and make the pathologic diagnosis of the patient and initiate pathogen-specific treatment. However, as evidenced by the data obtained, most patients waste time with repeated outpatient applications and unnecessary empiric antibiotic treatments. With each infestation, the extent of affected tissue in the breast increases, and the likelihood of local recurrence increases in this disease, for which there is no standard treatment regimen.

This study has several limitations. As it is a retrospective study, the same treatment algorithm could not be applied to all patients. This drawback could be eliminated if a prospective study and a standard algorithm were applied to IGM.

Conclusion

In conclusion, unnecessary repeated antibiotic treatment is performed in granulomatous mastitis. The unnecessary use of antibiotics is a global problem contributing to unnecessary costs, side effects, and antimicrobial resistance (20). We believe unnecessary antibiotic treatment should be avoided in patients with appropriate history and clinical features. That pathologic diagnosis should be made, and etiologic investigations should be given priority. In most cases, empiric antibiotic treatment is protracted because the necessary infrastructure and procedures are not clear to make a differential diagnosis in these patients. Since most IGM patients live in rural and third-world countries, access to diagnostic facilities and infrastructure is also difficult.

The lack of universal algorithms for diagnosis and treatment also creates difficulties. In the future, it will be beneficial to develop specific testing protocols, such as molecular methods, to distinguish infectious agents to expedite the diagnostic process for these patients. By improving the strategy for antibiotic use in these patients, it will be possible to reduce the unnecessary use of antibiotics.

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Conflict of interest statement

The authors declare no conflict of interest

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