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# Granulomatous Mastitis with Corynebacterium Infection

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ABSTRACT

**Background:** Idiopathic granulomatous mastitis (IGM) is a rare relapsing benign, chronic inflammatory breast disease characterized by infiltration of inflammatory cells including multinucleated giant cells. Recently, it has been suggested that infection with *Corynebacterium* species (spp.) may be involved in the onset of the disease. Therefore, the aim of this article is to summarize the previous IGM reports related to *Corynebacterium* spp.

**Methods:** I used the terms "granulomatous mastitis *Corynebacterium*" in PubMed and "granulomatous mastitis *Corynebacterium*" with Japanese in Google Scholar, which resulted in 63 English articles and 71 Japanese articles. I read all the abstracts and summarized the recent articles with *Corynebacterium* in the title.

**Results:** In 16 English articles and 4 Japanese ones, the most common *Corynebacterium* spp. was *Corynebacterium kroppenstedtii*, followed by *Corynebacterium tuberculostearium*.

**Conclusion:** *Corynebacterium* infection is widely detected with IGM. In addition to bacterial culture, real-time polymerase chain reaction and formalin-fixed, paraffin-embedded biopsy specimens' analysis can be used to detect *Corynebacterium* spp.



## INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare relapsing benign, chronic inflammatory breast disease characterized by infiltration of inflammatory cells including multinucleated giant cells, which was first described in 1972 by Kessler *et al*. as a mastitis presenting with multiple granulomas and abscess formation.[1] Although various causes have been proposed for granulomatous mastitis, its etiology is not clearly identified and both intrinsic and extrinsic factors are thought to be involved; therefore, it is considered to be "idiopathic".[2-5] The imaging and fine needle aspiration findings cannot completely distinguish between IGM and the breast malignancy; thus, histopathological diagnosis by core needle biopsy is essential for definitive diagnosis.[2,6-9]

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The following five criteria have been proposed by Carmalt *et al*. as diagnostic criteria for granulomatous mastitis.[10] 1) The women of childbearing age within 5 years of the last childbirth, 2) Infiltration of neutrophils and epithelioid histiocytes or lymphocytes, and granuloma formation with multinucleated giant cells, 3) Abscess formation, 4) lobular lesions, and 5) No evidence of caseous necrosis and Mycobacterium or fungal infections. Moreover, this disease was classified by Kaviani *et al*.[11]

IGM is considered to be a special form of galactophoritis. A hormonal imbalance such as hyperprolactinemia can be one of the causes of the breast inflammation.[12] Hyperprolactinemia can be induced and maintained by high doses of estrogen therapy, the use of oral contraceptives and antidepressants, thyroid dysfunction, or prolactinoma.[4,12-14] Therefore, even in the non-puerperal period, high blood levels of prolactin are thought to cause milk production followed by ductal ectasia leading to the rupture of the ducts and a persisting inflammation of

stromal cells, resulting galactophoritis.[12] IGM is considered as the final step of a pathophysiological process of these retention syndrome.[11]

The most common physical finding is a hard mass-like lesion with indistinct borders on palpation with pain.[4,6] Other symptoms including tenderness, erythema, skin thickening, sinus formation or axillary adenopathy may also be present.[2-4,6] Several imaging findings are reported as follows.[3,6,8,9] The most common mammographic finding showed a focal asymmetric density. The most common ultrasonographic findings showed a heterogeneous hypoechoic mass with irregular shape and an ill-defined margin. On dynamic contrast-enhanced MRI, the most frequent enhancement patterns were rim enhancement in masses. However, these imaging findings are similar to breast abscess and cancer; therefore, histopathological diagnosis is necessary.[3,6,9] If IGM is determined as a definite diagnosis, appropriate treatment should be given with caution to its associated diseases.

It has been suggested that infection with *Corynebacterium* species (spp.) may be involved in the onset of the disease since the isolation of the bacteria was first reported by Paviour *et al*. in 2002.[15] Therefore, the aim of this article is to summarize the previous IGM reports related to *Corynebacterium* spp.

## METHODS

The articles examined in this research were collected using the terms "granulomatous mastitis *Corynebacterium*" in PubMed and "granulomatous mastitis *Corynebacterium*" with Japanese in Google Scholar, which resulted in 63 English articles and 71 Japanese articles. I read all the abstracts and summarized the recent articles with *Corynebacterium* in the title.

## RESULTS.

We found 16 English articles,[15-30] and 4 Japanese ones (Table 1).[31-34] *Corynebacterium* (*C.*) *kroppenstedtii* was detected most frequently, followed by *C. tuberculostearicum*. *C. accolens* and *C. jeikeium* were reported only one article each.[16,21]

**Table 1.** Recent IGM articles with Corynebacterium in the title.

| Title | Author | Year | Patients number | Summary | Reference |
|---|---|---|---|---|---|
| Detection of *Corynebacterium kroppenstedtii* in Granulomatous Lobular Mastitis Using Real-Time Polymerase Chain Reaction and Sanger Sequencing on Formalin-Fixed, Paraffin-Embedded Tissues | Tariq *et al*. | 2021 | 67 | *Corynebacterium kroppenstedtii* was detected on formalin-fixed, paraffin-embedded tissues from 46 granulomatous lobular mastitis cases (68.7%) by real-time polymerase chain reaction. | 25 |
| Cystic neutrophilic granulomatous mastitis: *Corynebacterium* species-associated infection with distinct histology | Wang *et al*. | 2021 | 1 | Cystic neutrophilic granulomatous mastitis was linked to *Corynebacterium* species infection. | 30 |
| Negative pressure wound therapy of *Corynebacterium jeikeium* associated granulomatous mastitis | Maráz *et al*. | 2020 | 1 | Treatment-resistant granulomatous mastitis caused by *Corynebacterium jeikeium* was successfully treated with negative pressure wound therapy. | 22 |
| *Corynebacterium kroppenstedtii*: a challenging culprit in breast abscesses and granulomatous mastitis | Saraiya *et al*. | 2019 | Review | If granulomatous mastitis and breast abscess cases are recurrent, infection with *Corynebacterium kroppenstedtii* should be considered. | 24 |
| *Corynebacterium kroppenstedtii* in granulomatous mastitis: Analysis of formalin-fixed, paraffin-embedded biopsy specimens by immunostaining using low-specificity bacterial antisera and real-time polymerase chain reaction | Fujii *et al* | 2018 | 18 lesions | Real-time polymerase chain reaction using *Corynebacterium kroppenstedtii* genome from formalin-fixed, paraffin-embedded sections was demonstrated in 7 granulomatous mastitis lesions. | 18 |

| Title | Author | Year | Patients number | Summary | Reference |
|---|---|---|---|---|---|
| Two Cases of Granulomatous Mastitis Caused by infection with *Corynebacterium* spp. | Fujii *et al.* | 2018 | 2 | *Corynebacterium tuberculostearicum* and *Corynebacterium kroppenstedtii* were detected as the cause of granulomatous mastitis, respectively. | 31 |
| Cystic neutrophilic granulomatous mastitis with corynebacterium and staphylococcus mimicking breast carcinoma | Wang *et al* | 2018 | 1 | Cystic neutrophilic granulomatous mastitis mimicking carcinoma caused by two mixed bacteria including *Corynebacterium* species was reported for the first time. | 30 |
| Cystic neutrophilic granulomatous mastitis associated with *Corynebacterium* including *Corynebacterium kroppenstedtii* | Johnstone *et al.* | 2017 | 15 | *Corynebacterium kroppenstedtii* was identified from cystic neutrophilic granulomatous in nine cases. | 21 |
| The Brief Case: Recurrent Granulomatous Mastitis Due to *Corynebacterium kroppenstedtii* | Johnson *et al.* | 2016 | 1 | Matrix-assisted laser desorption ionization-time of flight mass spectrometry was a useful tool for identifying *Corynebacterium kroppenstedtii* and surgical intervention should be also considered for recurrent granulomatous mastitis. | 20 |
| A microbiological and clinical review on *Corynebacterium kroppenstedtii* | Tauch *et al.* | 2016 | Review | *Corynebacterium kroppenstedtii* is considered a potential human opportunistic pathogen and should be accurately identified in the clinical laboratory. | 26 |
| Cystic Neutrophilic Granulomatous Mastitis: Association With Gram-Positive Bacilli and *Corynebacterium* | Troxell *et al.* | 2016 | 35 | Biopsies from 19 patients demonstrated cystic neutrophilic granulomatous mastitis and *Corynebacterium* species were identified in three patients. | 28 |
| Antimicrobial Treatment Options for Granulomatous Mastitis Caused by *Corynebacterium* Species | Dobinson *et al.* | 2015 | 17 isolates from 16 patients | *Corynebacterium kroppenstedtii* (n = 11), *Corynebacterium tuberculostearicum* (n = 4), *Corynebacterium glucuronolyticum* (n = 1), and *Corynebacterium freneyi* (n = 1) were detected and investigated for antimicrobial resistance. | 17 |
| A Case of Granulomatous Mastitis Caused by an infection with *Corynebacterium Tuberculostearicum* | Kanazawa *et al.* | 2015 | 1 | Granulomatous mastitis caused by an infection with *Corynebacterium tuberculostearicum* is well controlled without aggravation for antimicrobial drugs. | 32 |
| Case of erythema nodosum associated with granulomatous mastitis probably due to Corynebacterium infection | Hida *et al.* | 2014 | 1 | Erythema nodosum was caused by granulomatous mastitis probably due to *Corynebacterium* infection. | 19 |
| A Case of Granulomatous Mastitis in which *Corynebacterium Kroppenstedtii* infection was Confirmed | Morimitsu *et al.* | 2013 | 1 | It was considered necessary in the treatment of granulomatous mastitis to conduct appropriate tests for *Corynebacterium kroppenstedtii* infection. | 33 |
| A case of granulomatous mastitis with | Shigematsu *et al.* | 2008 | 1 | *Corynebacterium kroppenstedtii* infection must be | 34 |

| Title | Author | Year | Patients number | Summary | Reference |
|---|---|---|---|---|---|
| *Corynebacterium Kroppenstedtii* infection | | | | considered in the treatment for patients with granulomatous mastitis. | |
| *Corynebacterium accolens* isolated from breast abscess: possible association with granulomatous mastitis | Ang *et al*. | 2007 | 1 | *Corynebacterium accolens* might be associated with granulomatous mastitis. | 16 |
| Granulomatous mastitis and corynebacteria: clinical and pathologic correlations | Methelin *et al*. | 2005 | 1 | Granulomatous mastitis might be caused by *Corynebacterium* species. | 23 |
| A clinicopathological review 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis | Taylor *et al*. | 2003 | 34 | *Corynebacterium* species were isolated from 52 of 116 microbiological specimens taken from the 34 cases and 14 were identified as *Corynebacterium kroppenstedtii*. | 27 |
| *Corynebacterium* species isolated from patients with mastitis | Paviour *et al*. | 2002 | 24 | *Corynebacterium* species including *Corynebacterium kroppenstedtii*, *Corynebacterium amycolatum*, and *Corynebacterium tuberculostearicum* were isolated from granulomatous lobular mastitis patients. | 15 |

## DISCUSSION

*Corynebacterium* spp. is a Gram-positive rod characterized by fat affinity. Hence, this organism is thought to cause infection in fatty mammary tissue. Therefore, it is necessary for appropriate methods of aseptic sampling of specimens and culture in a medium supplemented with Tween 80.[31] Although *Corynebacterium* spp. is susceptible to many antimicrobial agents, the usage of high fat-soluble antimicrobial agents such as macrolides, tetracyclines, and new quinolones is recommended because the mammary gland is a lipid-rich tissue. Doxycycline, amoxicillin, ciprofloxacin, and cefuroxime were reported for most common antimicrobials and favorable outcomes have been associated with long-term use. Moreover, there are no mortality rate in the clinical case of *C. kroppenstedtii* infection.[26] However, it has been suggested that fatty tissues in the mammary gland make it difficult for neutrophils to approach the organism and this may be the cause of the refractoriness of IGM.[31] On the other hand, it is difficult to exclude completely the possibility of the contaminations because some species of *Corynebacterium* spp. are normal, endogenous, bacterial flora of the skin and the breast.[19] Therefore, recent articles indicated not only bacterial culture but also real-time polymerase chain reaction (PCR) and formalin-fixed, paraffin-embedded (FFPE) biopsy specimens analysis for detecting pathogenically *Corynebacterium* spp.[18,25] It is reported that real-time PCR of *C. kroppenstedtii* from FFPE sections was useful (39-69% positive) in IGM cases.[18,25] The histopathological feature is granulomatous inflammation with dense exudation of lymphocytes, plasma cells, epithelioid histiocytes, multinucleated giant cells and neutrophils. The inflammation is accentuated in the lobule and/or around the mammary duct.[18,19,23,25] Non-caseating granulomas are often associated with neutrophilic infiltration to form suppurative granulomas.[15,18] Recently, cystic neutrophilic granulomatous mastitis with characteristic granulomas with central cystic spaces, in particular, has been considered to have *Corynebacterium* spp. infection.[28-30] Surgery may be indicated for some IGM patients with *Corynebacterium* infection that are resistant to common antibiotic therapies.[22]

## CONCLUSION

*Corynebacterium* infection is widely detected with IGM. In addition to bacterial culture, real-time PCR and FFPE biopsy specimens analysis can be used to detect *Corynebacterium* spp.

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## CONFLICT OF INTEREST

The author declares no conflicts of interest.

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