Cystic Neutrophilic Granulomatous Mastitis

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ABSTRACT

Granulomatous lobular mastitis (GLM) is an infrequent inflammatory breast disease, which can simulate malignancy on the basis of clinical and imaging features. It is typically found in parous or lactating women. The differential diagnosis of granulomatous mastitis includes infections caused by bacterial, fungal or mycobacterial agents, and autoimmune disorders like rheumatoid arthritis, sarcoidosis, giant cell vasculitis, and granulomatosis with polyangiitis. Cystic neutrophilic granulomatous mastitis (CNGM) is a sporadic sub-type of GLM that can be linked with infection with Gram-positive bacilli, specifically, *Corynebacterium*. It is characterised by lipogranulomas that comprise of "cystic" spaces lined by neutrophils which may contain Gram-positive rod-shaped bacteria. The majority of cases of GLM are still “idiopathic” as this pattern of inflammation still remains a mystery. We herein report three cases of CNGM and review the relevant literature.

Key Words: *Granulomatous mastitis, Corynebacterium, Gram-positive rods, Inflammatory breast disease, Cystic neutrophilic granulomatous mastitis.*

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INTRODUCTION

Cystic neutrophilic granulomatous mastitis (CNGM) is a recently described inflammatory breast lesion, presenting as granulomatous lesion comprising of small cystic spaces lined by inflammatory cells, which should be considered in the differential diagnosis of granulomatous mastitis.[1,2] This type of mastitis is usually ascribed to an infection caused by Gram-positive bacilli, named *Corynebacterium*.[2-4] These bacilli are easy to miss in routine laboratory smearing, staining, and cultures as they are scanty and not considered as usual cause of mastitis by clinicians or pathologists.[2]

We report three cases of inflammatory mastitis with suppurative granulomas representing CNGM.

CASE REPORTS

CASE 1:

A 33-year woman presented with a lump in the left breast for 9 months. Examination showed a lump in the upper inner quadrant of the left breast. The overlying skin was erythematous and ulcerated with cheesy material oozing from the lesion. There was no history of any known co-morbidity or trauma.

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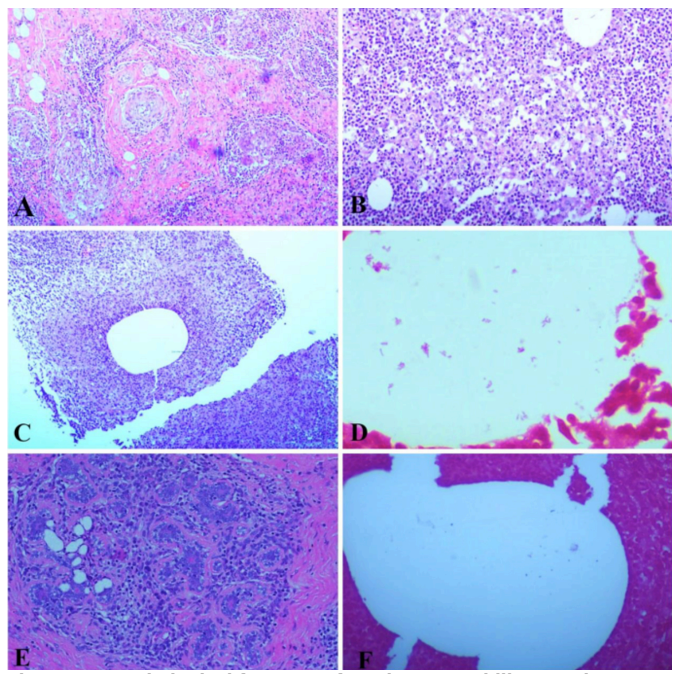

Figure 1: Morphological features of cystic neutrophilic granulomatous mastitis. H & E Section of breast core biopsy (A) granulomas composed of epithelioid cells with multinucleated giant cells and lymphocytes (B) cystic spaces were seen surrounded by neutrophils and giant cells (C) a single cystic space showed faint purple stained rod-like structure surrounded by an inflammatory infiltrate (D) Higher magnification of Gram-positive bacilli (E) Lobular mastitis showing chronic inflammatory infiltrate in a breast lobule (F) High power magnification of faint rod-like bacilli in a cystic space. H&E stain (A, B, C, E), Gram stain (D, F); original magnification: ×10 (A), ×20 (B, C, E, F), ×40 (D).

GeneXpert Mycobacterium tuberculosis (MTB) was not detected. Acid-fast bacilli (AFB) culture and smear were nega-

tive. Ultrasound examination of the breast showed a well-defined isoechoic area seen at 12 o'clock position measuring 0.5 × 0.4 cm. It showed a central cystic area with no vascularity on colour doppler ultrasound. It was reported as BIRADS III, probably a benign finding. An excisional biopsy of the lump was performed. Microscopic examination revealed granulomas composed of epithelioid cells with multinucleated giant cells and lymphocytes (Figure 1A). Cystic spaces were seen surrounded by neutrophils and giant cells (Figure 1B). Special stains, Periodic acid Schiff diastase (PAS-D) for fungus and Ziehl Neelsen (ZN) for AFB, were negative. The Gram stain of histopathological specimen was negative; however, the culture of pus was positive for *Corynebacterium spp.* A diagnosis of CNGM was made.

CASE 2:

A 31-year woman presented with right breast swelling for 2 months associated with pain and tenderness. There was a history of trauma to the breast 4 months back. Ultrasound showed dense echoes in the retro-areolar region measuring 2.2×1.2 cm with surrounding dilated ducts with parenchymal oedema. It was reported as BIRADS III, probably a benign finding. An ultrasound-guided trucut biopsy was performed and a pathologic examination revealed acute mastitis with a granulomatous component (Figure 1C). Occasional empty cystic spaces surrounded by neutrophilic abscesses were identified with faint rod-like structures (Figure 1D). These bacilli were positive on Gram stain. Scattered giant cells and a few foamy macrophages were also noted. Special stains, PAS-D for fungus and ZN for AFB, were negative. No specimen was sent for microbiological culture. A diagnosis of CNGM was made.

CASE 3:

A 35-year woman presented with swelling in the left breast for 1 month along with pain and fever. Ultrasound showed a collection of moving echoes seen from 11 to 7 o'clock position measuring approximately 6.3 × 2.6 cm, extending into the retro-areolar region. It was reported BIRADS III, probably a benign finding. A biopsy was done. Histopathologic examination revealed lobular mastitis (Figure 1E) showing granulomatous inflammation composed of epithelioid cells, lymphocytes, and plasma cells admixed with neutrophilic infiltrate. Multiple empty cystic spaces were identified surrounded by neutrophilic infiltrate. Special stains, PAS-D for fungus and ZN for AFB, were negative. A single cystic space showed a faint purple stained rod-like structure on Gram-stain (Figure 1, F). Pus was sent for microbiological culture which was negative. A diagnosis of CNGM was made.

DISCUSSION

Inflammatory breast diseases are most frequently observed in females of reproductive age especially lactating women with clinical symptoms of pain, erythema and lump formation. Due to non-specific radiographic findings, histopathological examination is of utmost importance for an accurate diagnosis.[5,6] Usually antimicrobials are prescribed for such clinical conditions, at least initially, but surgical removal may be necessary for complicated infections when there is abscess formation.[5]

Granulomatous lobular mastitis (GLM) is a rare type of inflammatory mastitis which occurs in women of reproductive age. GLM shows radiological features of mastitis.[3,7] Granulomas with cystic cavities lined by neutrophils (possibly representing dissolved lipids) are observed in a few cases of GLM. This characteristic pattern was illustrated by Taylor *et al*. in two other series in which an association of GLM was made with *Corynebacterium* infection.[1,3,4] In Taylor and colleagues' study, Gram-positive rods (GPRs) were identified in 14 cases and the organisms were found exclusively in cystic cavities lined by neutrophils within the granulomas.[3,5] This unique pattern was named CNGM by Renshaw *et al*.[4] All three cases in Renshaw *et al*.'s study had histopathologic features of CNGM with GPRs confined in cystic vacuoles rimmed by neutrophils. The most peculiar thing about these cases was that they had negative microbiological cultures.[3] Microbiologically, *Corynebacterium kroppenstedtii*, a rare bacteria having an affinity for lipids with the breast being its favoured site for growth and multiplication, is considered to be the most commonly identified pathogen in CNGM.[6] Microbiological and histopathological diagnosis of mastitis related to *Corynebacterium* infection is very challenging due to the under-appreciation of this rare entity.[6] GPRs, especially *Corynebacterium* species, are easily missed in histopathologic examination and microbiological cultures as they are very scanty in specimens and difficult to grow on cultures.[1]

Usually disregarded as skin or environmental contaminant, *Corynebacterium*, is not given much importance in laboratory settings, which leads to a lack of knowledge of this pathogen associated with GLM.[2,8] Infections with *Corynebacterium* are so rare that the current data for clinical antibiotic susceptibility testing methods and breakpoints is scanty for validation and clinical correlation. However, there are reports of emerging drug-resistant strains of this particular species.[8] It is of utmost importance to study and understand this pattern of mastitis related to GPRs for timely diagnosis and appropriate antibiotic therapy to ensure positive outcomes. The pattern of inflammation is unusual and the likelihood of yielding the causative pathogen in the laboratories is difficult. After excluding all the causative agents from differentials, the pathologists should consider the possibility of *Corynebacterium* infection even with a negative Gram-stain.[8]

In these cases, empty cystic cavities within the granulomas were evident. The clinical presentation and histologic features along with microbiologic correlation in these cases were characteristic of CNGM. All three cases showed granulomatous inflammation composed of epithelioid cells, lymphocytes, and plasma cells admixed with neutrophilic infiltrate. Neutrophils were seen lining the cystic cavities. Occasional scattered giant cells and foamy macrophages were seen. GPRs were noted in two cases. Microbiological cultures were sent in two cases, out of which, one was positive for GPRs. Radiological features in these cases were mostly benign suggesting BIRAD-III lesion. Since tuberculosis (TB) is endemic in our country, granulomatous inflammation is mostly treated by physicians as TB; however, CNGM is a newly described entity and should be considered in the differen-

tial diagnosis of granulomatous inflammatory lesions of the breast.

In conclusion, GPRs are an important cause of granulomatous mastitis which should not be overlooked. Clinical awareness of CNGM should be raised among radiologists, infectious disease consultants, and surgeons in collaboration with microbiologists and histopathologists for appropriate diagnosis and timely management of this rare infectious disease.

PATIENTS' CONSENT:
Informed consent were obtained from the patient to publish the data concerning this case.

COMPETING INTEREST:
The authors declared no competing interest.

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