International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(3): 23-25
Received: 09-05-2021
Accepted: 12-06-2021

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Cystic neutrophilic granulomatous mastitis: A case report

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DOI: https://doi.org/10.33545/pathol.2021.v4.i3a.384

Abstract
Cystic neutrophilic granulomatous mastitis [CNGM] is a recently characterized entity, with specific histopathological details that differentiate it from other types of chronic idiopathic mastitis. The presence of gram-positive bacilli within cystic-like spaces surrounded by neutrophils, in a context of suppurative granulomatous inflammation, define this entity. The importance of its recognition in the diagnostic report lies in its association with infection by corynebacterial species, so that treatment with antibiotics can be targeted. Here we present a case of CNGM of left breast in a 34-year-old female.

Keywords: cystic neutrophilic granulomatous mastitis, gram positive bacilli, corynebacteria, chronic mastitis

Introduction
Inflammatory mastitis is more frequently found in women of childbearing age, who are breastfeeding, that report clinical symptoms of pain, erythema, and swelling. Mastitis is usually classified by duration and inflammatory infiltrate, and includes acute-neutrophilic, subacute-granulomatous, and chronic-lymphocytic/ plasma mastitis. The potential causes of this spectrum of diseases are variable and can include both infectious and non-infectious (autoimmune) and idiopathic inflammatory mechanisms. Granulomatous lobular mastitis is a rare subtype of mastitis. This entity can be present as painful palpable breast masses that range from 1 to 10 cm in size. Despite extensive clinical, imaging, pathological, and microbiological studies, a subgroup of patients with this entity remains undetermined of a specific etiology. Patients are sometimes labeled as "idiopathic granulomatous lobular mastitis" [1].
First described in 1972, granulomatous mastitis is a rare inflammatory breast disease of unclear etiology. It most commonly affects parous women of reproductive-age and presents as a tender, enlarging breast mass, which may be complicated by sinus and abscess formation. Granulomatous mastitis is histologically characterized by granulomas in and around lobules, often with suppuration and sometimes associated micro abscess formation. An association between corynebacteria infection and granulomatous mastitis was proposed by a clinicopathological review of 34 patients in New Zealand in 2003 [2].

Case report
A 34- year-old female presented with a mass in her left breast with pus discharge for 10 days. Ultrasonography [USG] examination revealed an irregular mass suspicious of breast carcinoma or an abscess and the clinical suspicion was an antibioma. Left breast biopsy was done and we received tissue pieces aggregating 2 x 1 x 1cm, firm in consistency with on whitish yellow cut surface.
Microscopic examination of Hematoxylin and Eosin [H&E] stained serial sections revealed [Fig 1, 2 A] multiple granulomas composed of histiocytes, foreign body giant cells, few langhans giant cells and lymphocytes. Majority of granulomas were admixed with plenty of neutrophils surrounding centrally placed cystically dilated spaces of variable sizes but larger than surrounding adipocytes.
Special stains like Gram stain, PAS [Periodic acid] stain and Fitefaraco stains were also done for detection of bacterial, mycobacterial, and fungal infections respectively. Very few granulomas showed [Fig 2; B]: gram positive bacilli in the center of cystic spaces. However

[Fig 2; C, D] the PAS and Fitefaraco stains were negative for fungi and acid-fast mycobacteria respectively.

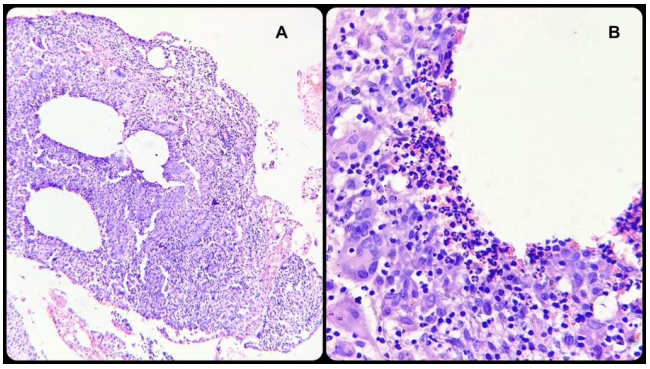

Fig 1: Granulomatous mastitis with suppuration and cystic spaces: showed cystic spaces surrounded by plenty of neutrophils, epithelioid cells, langhans giant cells, foreign body giant cells and lymphocytes. [H&E: A:10X; B:40X]

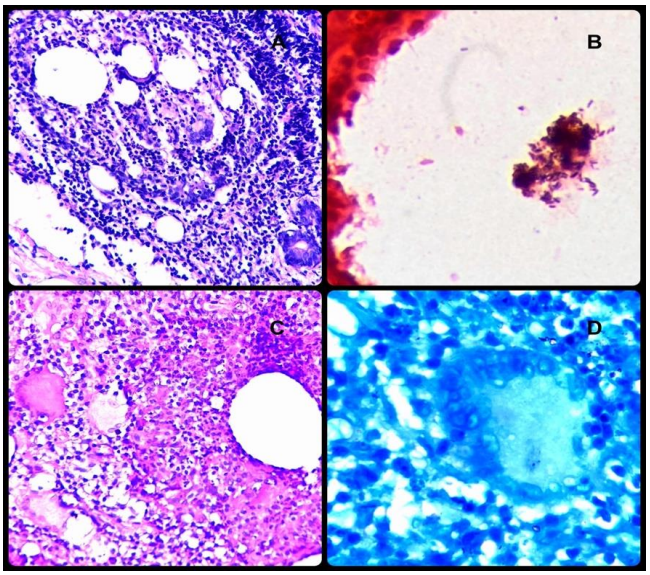

Fig 2: A: Granulomatous mastitis: showing granuloma formation with normal acini at the periphery. [H&E: 10X] **B:** Showing Gram positive bacilli lying in the cystic spaces. [Gram Stain: 40X] **C:** Showing a granuloma which negative for fungus [PAS: 10X] **D:** Shows a granuloma which is negative for acid fast bacilli. [Fitefaraco: 40X].

Discussion

Granulomatous mastitis is a rare inflammatory breast disease that typically presents as a painful mass. The differential diagnosis for granulomatous mastitis is broad and includes fungal or mycobacterial infection and autoimmune conditions such as sarcoidosis, vasculitis (giant cell, polyarteritis, granulomatosis with polyangiitis), rheumatoid arthritis. Granulomatous inflammation on biopsy can also be secondary to squamous metaplasia of nipple ducts (SMOLD; also termed Zuska disease), infarction or fat necrosis, or associated with an occult carcinoma. Nevertheless, a large proportion of cases remain unexplained; hence the terminology "idiopathic granulomatous mastitis" is often used [3].

CNGM is a distinct histologic pattern within the entity described as "granulomatous mastitis" [4]. Granulomatous inflammation with suppuration and vacuolated spaces, consistent with dissolved lipid, surrounded by neutrophilic inflammation. This pattern has been termed cystic neutrophilic granulomatous mastitis [CNGM] [2]. Clinically and radiologically CNGM can mimic carcinoma. The lesion usually occurs in women of reproductive age and may be associated with lactation or occur in the postpartum period. In addition, it can persist or recur leading to abscess and sinus tract formation [4].

The role of Corynebacterium, a Gram-Positive bacillus, in invasive infections is often discussed since most of these species are part of the endogenous skin flora [5]. The link between Corynebacterium and granulomatous mastitis has been reported periodically since the publication of the case series by Taylor and collaborators in 2003 [6]. Gram-positive bacteria are identified within the cystic spaces, with several studies supporting Corynebacterium species as the infectious agent involved, usually Corynebacterium kroppenstedtii although Corynebacterium amycolatum has also been reported [7]. For its differential diagnosis, special stains such as Zeihl Nielsen are performed to rule out acid-fast bacilli and PAS and to rule out fungi [8].

Although we were able to identify gram-positive bacilli. Nevertheless, while these bacteria may represent Corynebacterium, other gram-positive bacilli, such as Propionibacterium or Clostridium species could not be ruled out. However, the histologic features we report are like those described by Taylor *et al*. In addition, to our knowledge, the most common bacterium that has been documented to have granulomas associated with it in breast abscesses is Corynebacterium. Finally, there are also several other case reports describing cases of Corynebacterium infection in the breast, suggesting that this is not an uncommon pathogen in this site. Regardless of the exact species, recognition of this pattern of gram-positive bacillus infection is important for several reasons. First, many gram-positive species such as Corynebacterium are hard to grow. Second, the organisms are very easy to miss. They are rare and present only in the cystic spaces, not the inflammation in between. Pathologist who is unaware of this pattern of inflammation may easily look for organisms in the wrong parts of the slide. Finally, because the pattern of inflammation with cystic spaces is so distinctive and the likelihood of identifying the organism is so low in many laboratories, once the possibility of a mycobacterial infection has been excluded, pathologist should raise the possibility of gram-positive bacillus or even corynebacterial infection even in the face of a negative Gram stain. Gram-positive bacilli infections have a distinctive pattern of inflammation in breast abscesses that can easily be overlooked. General pathologists should be aware of the distinctive features of this infection in breast abscesses and should actively search for gram-positive bacilli in distinctive cystic spaces [9].

Conclusion

The distinct histological features of granulomatous inflammation with acute inflammation and cystic spaces should prompt careful search for rare Gram-positive bacilli within these spaces. Microbiological investigation for corynebacteria, including C. kroppenstedtii, should be instigated in the presence of these suggestive histological features. This may require special culture techniques and/or 16S rRNA gene sequencing [2].

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