

CASE REPORT

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Cystic neutrophilic granulomatous mastitis during chemotherapy treatment for invasive breast carcinoma – a rare lesion that simulates tumor progression

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Abstract

Background: Cystic neutrophilic granulomatous mastitis (CNGM) is an uncommon and recently described pattern of granulomatous mastitis. To our knowledge, no cases have been described during chemotherapy for invasive breast cancer.

Case presentation: A 42-year-old female patient had a diagnosis of invasive breast carcinoma (3-cm nodule). During neoadjuvant chemotherapy, she presented with an enlargement of the breast nodule that measured 7.0-cm on palpation. The lesion did not show typical inflammatory clinical findings and simulated tumor progression. A core biopsy showed granulomas with pseudocystic spaces with gram-positive bacilli (*Corynebacterium* sp.), and numerous circumjacent neutrophils. She was treated with antibiotics and resumed chemotherapy. Surgical specimen showed a 1.0-cm residual carcinoma and extensive xanthogranulomatous inflammation with no evidence of residual CNGM.

Conclusion: CNGM is usually associated with typical clinical presentation of mastitis. It is an important pattern of granulomatous inflammation to be recognized in the breast since it directly impacts treatment. The present case highlights its potential occurrence during chemotherapy treatment of breast cancer mimicking progression of breast malignancy.

Keywords: Mastitis, Breast neoplasms, *Corynebacterium*

Backgrounds

Cystic neutrophilic granulomatous mastitis (CNGM) is an uncommon and recently described pattern of granulomatous mastitis (D'Alfonso et al. 2015; Johnstone et al. 2017; Gautham et al. 2019; Wu and Turashvili 2020). No cases have been described during chemotherapy for

invasive breast cancer. To the best of our knowledge, only a similar but not identical case of a 50-year-old female patient presented CNGM 3 years after treatment of breast cancer by surgery, chemotherapy and radiation therapy (Troxell et al. 2016) has been reported previously.

CNGM is rare and diagnosed in less than 1% of all breast specimens. It is characterized by suppurative lipogranulomas composed of central lipid vacuoles with surrounding neutrophils and an outer cuff of epithelioid histiocytes. Some of the lipid vacuoles may show gram-positive bacilli usually documented as *Corynebacterium*

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sp. It occurs in parous women with a mean age of 35 years (Wu and Turashvili 2020).

Case presentation

A 42-year-old female patient sought medical assistance due to a palpable nodule in the right breast noted 3 months earlier. She had history of three pregnancies, two children and one abortion – first son at 27-year and 5 years of lactation. She had no history of previous breast disease, familial history of breast cancer or use of exogenous hormones. At physical examination, a firm nodule was palpable at the upper outer quadrant of the right breast and one enlarged lymph node at the right axilla. The ultrasonography showed BI-RADS 4c lesion and magnetic resonance imaging revealed a 3-cm irregular nodule (type III curve) and a 2.4-cm axillary lymph node (Fig. 1). A core biopsy yielded a diagnosis of invasive breast carcinoma of no special type, Nottingham histologic grade 3, ER positive (15–20%), PR positive (1–2%), HER2 negative (0 score), Ki67: 70–75%. Fine-needle aspiration of the axillary lymph node was negative for malignancy.

The patient was treated with neoadjuvant chemotherapy with Doxorubicin and Cyclophosphamide (AC) dose-dense (with prophylactic granulocyte colony-stimulating factor) for 4 cycles, followed by weekly Paclitaxel plus Carboplatin for 12 cycles. It was noted a reduction of the breast nodule on palpation after the first two cycles of AC protocol. The patient did not develop neutropenia during chemotherapy. After the third cycle of Paclitaxel and Carboplatin treatment, she presented with an enlargement of the breast nodule that measured 7.0-cm on palpation, localized in the upper outer quadrant and transition between outer quadrants. The lesion

did not show typical inflammatory clinical findings, and simulated tumor progression (Fig. 2a, b, c). A new core biopsy showed granulomas with pseudocystic spaces with gram-positive bacilli (*Corynebacterium* sp.), and numerous circumjacent neutrophils (Fig. 3a–f). Special stains were negative for fungi and acid-fast bacilli. The patient was treated with Clindamycin and Ciprofloxacin for seven days, resumed chemotherapy program and was submitted to breast-conserving surgery with oncoplastic technique, plus sentinel lymph node biopsy and contralateral breast symmetrization. Surgery was performed 3 weeks after the end of neoadjuvant chemotherapy. The pathology study of the surgical specimen showed a residual 1.0-cm invasive breast carcinoma of no special type Nottingham histologic grade 3 – AJCC partial response (Fig. 2d), in a tumor bed of 3-cm that showed extensive areas of xanthogranulomatous inflammation (Fig. 4), with foreign body type giant cells, suppurative inflammation, with three negative axillary lymph nodes. There were no residual areas of cystic neutrophilic granulomatous mastitis, no gram-positive bacteria, fungi or acid-fast bacilli were detected. On follow up (53 months), the patient is using ovarian suppression with an aromatase inhibitor. She has no evidence of active cancer disease or signs or imaging findings of mastitis. Patient follow-up includes mammography and annual breast ultrasound, and both are without pathological findings.

Discussion

CNGM is typically unilateral (< 10% bilateral) and the most common clinical findings are breast mass (53%), pain (12%), abscess (12%) nipple discharge (11%) and erythema (11%). Ultrasound is the preferred imaging

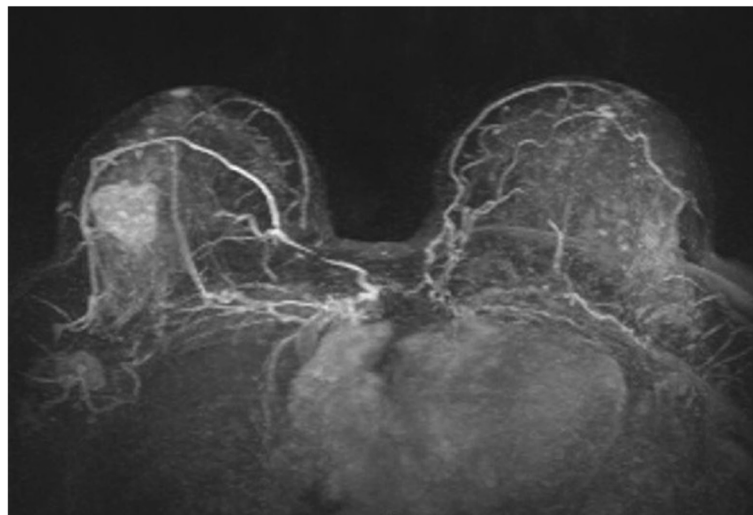


Fig. 1 Magnetic resonance imaging (prior to first biopsy). The right breast shows a dense nodule with irregular contours and heterogeneous contrast enhancement

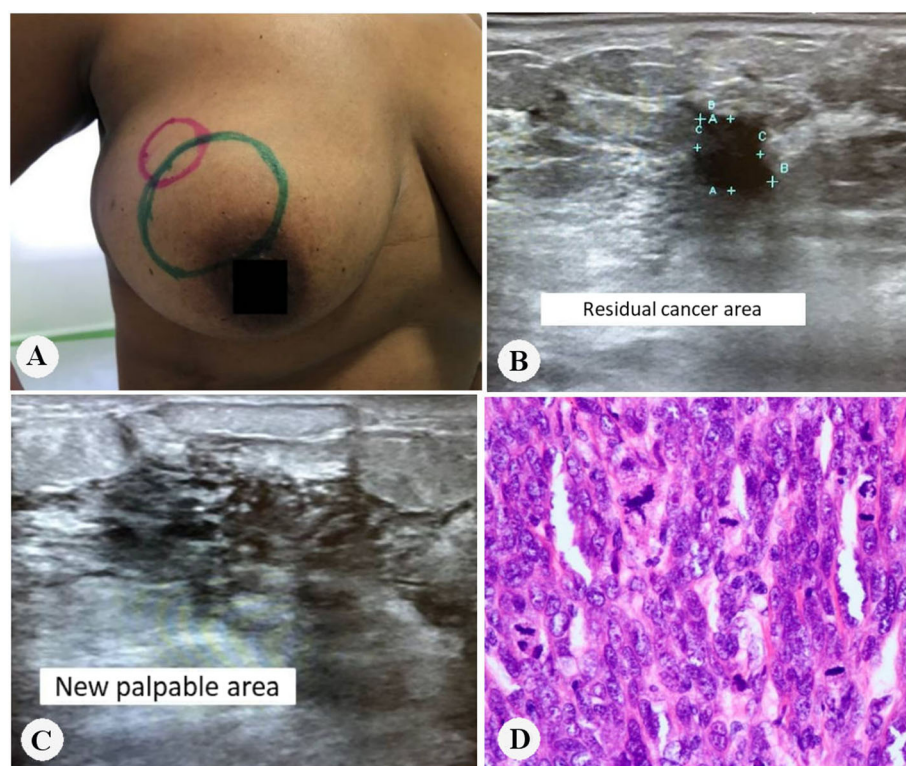


Fig. 2 A 7.0-cm tumor in the upper outer quadrant and transition between outer quadrants, without typical inflammatory clinical findings (green circle) next to the residual nodule after neoadjuvant chemotherapy (pink circle) (a). Ultrasonography appearance of the residual nodule (corresponds to que pink circle in figure (a)) (b) and the new “tumor” area (corresponds to que green circle in figure (a)) (c). In d, the residual tumor shows frequent mitoses and high-grade cytology and architecture (HE, 400x)

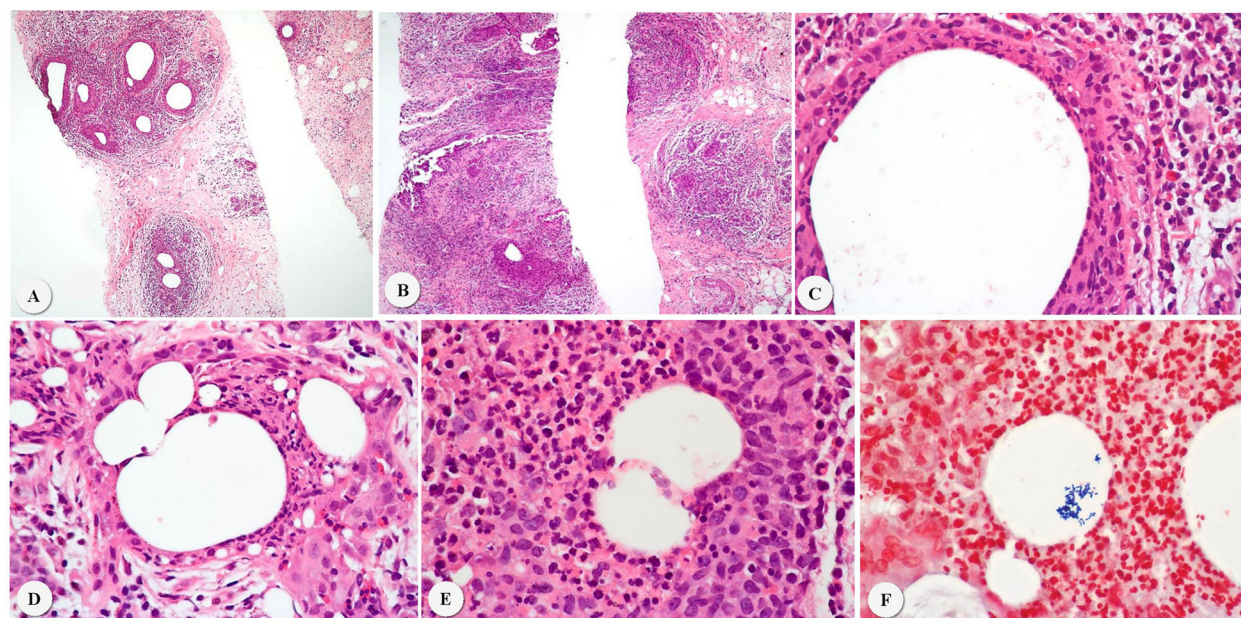


Fig. 3 Core biopsy of the 7-cm mass in the right breast: non-necrotizing granulomas with mixed lobulocentric infiltrate (rich in neutrophils) associated with pseudocystic spaces (a-e). Gram-positive bacilli in Gram stain (400x) (f)

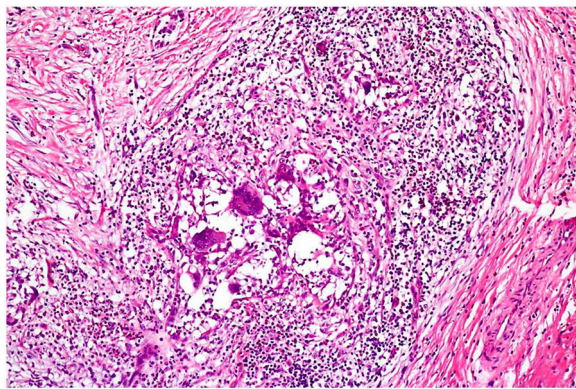


Fig. 4 Extensive areas of xanthogranulomatous reaction in the surgical specimen (HE, 100x)

test and has shown mass (72%), duct dilatation (11%), abscess (6%), edema (6%) and fluid collection (6%). Mammography usually shows mass or asymmetry and 60% of all cases evaluated for Breast Imaging Reporting and Data System were categorized as BI-RADS 4 (suspicious of malignancy) (Wu and Turashvili 2020).

CNGM is a distinctive morphologic form of granulomatous lobular mastitis that shows granulomas with pseudocystic spaces containing numerous circumjacent neutrophils and is more commonly associated with the presence of *Corynebacterium* sp. (Renshaw et al. 2011; Troxell et al. 2016; Shoyele et al. 2018). Gram positive bacteria can be detected in 58% of all cases of CNGM (Wu and Turashvili 2020). In a recent series of 19 cases, Sangoi reported that thicker sections (6 μ m) for Gram stain improved detection from 37 to 58% (Sangoi 2020). *Corynebacterium* species are difficult to culture and the ability to isolate them in series of CNGM ranged from 17 to 93% (Wu and Turashvili 2020). Pathologists play an important role on identifying this unique pattern of granulomatous mastitis. Even though typical gram-positive bacilli may not always be found, CNGM should be rendered on morphologic basis and commented.

Granulomatous lobular mastitis is an idiopathic and uncommon condition that usually affects women after delivery (with a mean interval of 2 years) and may simulate abscess or malignancy on clinical and imaging evaluations. Granulomatous lobular mastitis is centered in lobules, may show poorly formed granulomas, and is usually associated with dense inflammatory infiltrate with plasma cells, fat necrosis and abscesses. In contrast, sarcoidosis shows widespread distribution of well-formed granulomas and lacks extensive associated inflammation or necrosis and abscesses. Mammary duct ectasia is a inflammatory process centered on ducts that may show giant cells but lacks well-formed granulomas and does not have strong association with postpartum. In puerperal, there is association with recent delivery

and bacterial infection can be documented (Hoda et al. 2014). Among infectious causes of granulomatous inflammation in the breast, well known etiologies are tuberculosis and cat scratch disease (Hoda et al. 2014). Fungal and parasites are also possible etiologic agents (Illman et al. 2018). In such cases, clinicopathological correlation is helpful and definite diagnosis relies on direct detection of microorganisms. Other mechanisms for granulomatous lesions of the breast include reaction to oral contraceptives, reaction to foreign materials, autoimmunity, and local reaction to extravasated secretion of mammary glands.

Chemotherapy-induced neutropenia is common and low absolute neutrophil count (< 500 cells/mm³) develop in up to 37% of all breast cancer patients during adjuvant chemotherapy. This side effect is associated with life-threatening infections and may lead to chemotherapy dose reductions or delays that may reduce the relative dose intensity, thus impacting on early and long-term outcomes (Crawford et al. 2004; Fontanella et al. 2014). In the present case, the patient used prophylactic granulocyte colony-stimulating factor (Weycker et al. 2019; Papakonstantinou et al. 2020) and did not develop neutropenia during neoadjuvant treatment. Mastitis is not a common site of infection among neutropenic breast cancer patients.

Conclusion

Cystic neutrophilic granulomatous mastitis is an uncommon and recently described pattern of granulomatous mastitis. The present case highlights its potential occurrence during chemotherapy treatment of breast cancer mimicking progression of breast malignancy. It is an important pattern of granulomatous inflammation to be recognized in the breast since it directly impacts treatment.

Abbreviations

CNGM: Cystic neutrophilic granulomatous mastitis; ER: Estrogen receptor; HE: Hematoxylin and eosin stain; PR: Progesterone receptor; BI-RADS: Breast Imaging Reporting and Data System

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Adherence to national and international regulations

Not applicable.

Authors' contributions

JRF conceived the idea. DAA and JRF were the major contributors to the writing of the manuscript. LB participated in the surgical treatment surgery. ML participated in the clinical treatment. JRF and MFS diagnosed the case. MFS, ML, and LB were major contributors for critically revising the manuscript for important intellectual content. The author(s) read and approved the final manuscript.

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Ethics approval and consent to participate

Written informed consent was obtained from the patient for participation in the study.

Consent for publication

Written informed consent was obtained from the patient for participation in the study.

Competing interests

The authors declare that they have no competing interests.

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References

- Crawford J, Dale DC, Lyman GH (2004) Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer* 100:228–237
- D'Alfonso TM, Moo TA, Arleo EK, Cheng E, Antonio LB, Hoda AS (2015) Cystic neutrophilic granulomatous mastitis: further characterization of a distinctive histopathologic entity not always demonstrably attributable to *Corynebacterium* infection. *Am J Surg Pathol* 39(10):1440–1447
- Fontanella C, Bolzonello S, Lederer B, Aprile G (2014) Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. *Breast Care (Basel)* 9:239–245
- Gautham I, Radford DM, Kovacs CS, Calhoun BC, Procop GW, Shepardson LB, Dawson AE, Downs-Kelly EP, Zhang GX, Al-Hilli Z, Fanning AA, Wilson DA, Sturgis CD (2019) Cystic neutrophilic granulomatous mastitis: the Cleveland Clinic experience with diagnosis and management. *Breast J* 25(1):80–85
- Hoda SA, Brogi E, Koerner FC, Rosen PR (2014) Rosen's breast pathology, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 47–55
- Illman JE, Terra SB, Clapp AJ, Hunt KN, Fazzio RT, Shah SS, Glazebrook KN (2018) Granulomatous diseases of the breast and axilla: radiological findings with pathological correlation. *Insights Imaging* 9:59–71
- Johnstone KJ, Robson J, Cherian SG, Wan Sai Cheong J, Kerr K, Bligh JF (2017) Cystic neutrophilic granulomatous mastitis associated with *Corynebacterium* including *Corynebacterium kroppenstedtii*. *Pathology* 49(4):405–412
- Papakonstantinou A, Hedayati E, Hellström M et al (2020) Neutropenic complications in the PANTHER phase III study of adjuvant tailored dose-dense chemotherapy in early breast cancer. *Acta Oncol* 59:75–81
- Renshaw AA, Derhagopian RP, Gould EW (2011) Cystic neutrophilic granulomatous mastitis: an underappreciated pattern strongly associated with gram-positive bacilli. *Am J Clin Pathol* 136(3):424–427
- Sangoi AR (2020) "Thick section" gram stain yields improved detection of organisms in tissue sections of cystic neutrophilic granulomatous mastitis. *Am J Clin Pathol* 153(5):593–597
- Shoyele O, Vidhun R, Dodge J, Cheng Z, Margules R, Nee P, Sieber S (2018) Cystic neutrophilic granulomatous mastitis: a clinicopathologic study of a distinct entity with supporting evidence of a role for *Corynebacterium*-targeted therapy. *Ann Diagn Pathol* 37:51–56
- Troxell ML, Gordon NT, Doggett JS, Ballard M, Vetto JT, Pommier RF, Naik AM (2016) Cystic neutrophilic granulomatous mastitis: association with gram-positive bacilli and *Corynebacterium*. *Am J Clin Pathol* 145(5):635–645
- Weycker D, Doroff R, Hanau A, Bowers C, Belani R, Chandler D, Lonshteyn A, Bensink M, Lyman GH (2019) Use and effectiveness of pegfilgrastim prophylaxis in US clinical practice: a retrospective observational study. *BMC Cancer* 19:792
- Wu JM, Turashvili G (2020) Cystic neutrophilic granulomatous mastitis: an update. *J Clin Pathol* 73:445–453

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