ABS ANNALS OF BREAST SURGERY
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Peer Review File

Article information: http://dx.doi.org/10.21037/abs-20-155

Reviewer A

Comment 1: Possibility, there's more than 5 male granulomatous mastitis cases in the literature, as pointed out on the manuscript. For instance, I published a paper on 2020 that out of 90 cases of granulomatous mastitis, 3 were men (2 idiopathic). Title of the paper: Granulomatous mastitis: etiology, imaging, pathology, treatment, and clinical findings. A deeper literature search for additional male GM would be recommended, although I agree that is the first case of BILATERAL male GM in the literature.

Reply 1: The criteria we used for the literature search was to count male cases of Idiopathic granulomatous Mastitis (IGM) only if explicitly described as idiopathic granulomatous mastitis in the text. This was done to maintain consistency with other recently published papers including a May 2020 paper by Sahin et. al "Idiopathic granulomatous mastitis in a male breast following intravesicle Bacille Calmette-Guerin treatment" which quoted 3 cases using this principle and we were able to find an additional case since then, to total 5. The reviewer's paper was reviewed during the literature search however, we could not be certain that the two cases were idiopathic as it was not explicitly stated. However, we do acknowledge that additional cases may have been missed, therefore, we have revised our text to a more general statement which will allow for the possibility of additional cases in the literature.

Changes in the text: We have modified our text from **"**There are only 5 reported cases of IGM in males." to "There **are a few** reported cases of IGM in males. To the best of our knowledge, this is the first case of bilateral disease" (**see p3, line 68 and p5, line 136**). We have also modified the Abstract accordingly **(see p2, line 29).**

Comment 2:
The majority of male idiopathic GM cases, some hyperestrogenism (or other feminizing hormone increased serum level) state was found (exogenous or endogenous, criptorchidism, etc…), which may theoretically result in GM in the male population. Is the patient in the manuscript under any hyperhormonal state, or have any condition that would predispose him for increased hormone levels?

Reply 2: The patient has no known condition that would predispose him to increased hormonal levels (exogenous or endogenous) nor did he present with any clinical symptoms suggestive of hyper-estrogenism state.

Please note that we have revised the text to clarify that the patient presented with **purulent peri-areolar discharge from sinus tracts** and NOT true nipple discharge/galactorrhea. Also, the patient had **no formal diagnosis of gynecomastia** pre-dating this presentation but rather described a long-standing history of a waxing and waning lump in his left chest.

Changes in the text:

1. All instances of "nipple" discharge have been replaced with "peri-areolar discharge from sinus tracts" **(see p2, line 30-31; p3, line 74; p5, line 118; p7, 178).**
2. We have also removed **"gynecomastia"** from the patient's medical history in the Case Presentation section **(see p4, line 77).**
3. We have added the following statement to the Discussion section as a limitation **"Unfortunately, an endocrinological work-up or prolactin level was not performed, which may have been relevant." (see p6, line 159-161).**

Comment 3: In multiple literature papers, it was shown some predisposition for some specific ethnic group versus others to develop GM, regardless of sex. Would that be relevant for this manuscript to describe the ethnical group of the patient?

Reply 3: Given that there is some clinical relevance as you have stated, we have included the patient's ethnical background.

Changes in the text:
In the Case Presentation section, we have added the patient's ethnical background to the text as follows; "**His ethnic origin is identified as black.**" **(see p4, line 78-79).**

Reviewer B

This case study is an interesting report of a disease rarely encountered in men. It appears to be the sixth reported case in the English literature of granulomatous mastitis (GM) in a male. The report is well written.

I have a few minor comments:

Comment 1: Line 52: ….usually affects parous women….

Reply1: We have modified our text as advised.

Changes in the text: Text has been changed as follows:

Revised text p3, line 54: "…usually affects **parous women**".

The Abstract has also been revised accordingly **(see p2, line 28).**

Comment 2: Line 53: …elevated hormonal levels, particularly prolactin….

Reply 2: We have modified our text as advised.

Changes in text: Text has been changed as follows:
Revised text p3, lines 55-56: "…elevated hormonal levels, particularly prolactin."

Comment 3: Line 55: I think the authors should acknowledge that several case series (not just case reports) have demonstrated that bacterial infection, typically Corynebacterial spp is often associated with GM, and this should be the main diagnostic consideration in a case of GM. This infection has a classic histologic pattern termed cystic neutrophilic granulomatous mastitis (CNGM). The authors have cited (ref 3) a seminal study from New Zealand describing CNGM with 34 cases, an example of a larger series.

Reply 3: Thank you for highlighting this point. We do acknowledge this and have modified the text as advised.

Changes in text: We have removed "a few case reports". The revised text now reads as follows;
Revised text p3, lines 57-59: "More recently, Corynebacterium, a gram-positive bacillus endogenous to the skin, has been shown to be associated with IGM and that this organism…". We have also added a statement about the histologic pattern observed with Corynebacterium infection as follows:
Revised text p3, line 61-62: "This infection demonstrates a distinct histologic pattern of cystic neutrophilic granulomatous mastitis (CNGM)."

Comment 4: Line 101: The authors should note that a pattern of CNGM was not demonstrated in their patient's breast biopsy/excision.

Reply 4: We confirm that CNGM was not demonstrated in the patient's breast biopsy and this has been highlighted in the text.

Changes in text: We have added to the text, "A histologic pattern of CNGM was not demonstrated on any of the breast biopsy samples" **(see p5, line 112).**

Comment 5: I think the authors should comment on whether any specific work up to exclude an underlying endocrinopathy was performed.

Reply 5: Unfortunately, no specific work up to exclude an underlying endocrinopathy was done, although this may have been relevant. We have added this limitation in our Discussion section. Of note, at the time of presentation, the patient had no medical history or known condition that would predispose him to increased hormonal levels nor did he present with any clinical symptoms suggestive of hyper-hormonal state.

Please note that we have revised the text to clarify that the patient presented with **purulent peri-areolar discharge from sinus tracts** and NOT true nipple discharge/galactorrhea. Also, the patient had **no formal diagnosis of gynecomastia pre-dating this presentation** but rather described a long-standing history of a waxing and waning lump in his left chest.

Changes in the text:

1. All instances of "nipple" discharge have been replaced with "peri-areolar discharge from sinus tracts" **(see p2, line 30-31; p3, line 74; p5, line 118; p7, 178).**
2. We have also removed **"gynecomastia"** from the patient's medical history in the Case Presentation section **(see p4, line 77).**
3. We have added the following statement to the Discussion section as a limitation **"Unfortunately, an endocrinological work-up or prolactin level was not performed, which may have been relevant." (see p6, line 159-161).**

Reviewer C

Comment 1: p5, line 116-117: consider revising to ' most common clinical finding on physical examination', consider revising to solitary tender palpable lump (exclude unilateral and subareolar).

Reply 1: We have revised the text as suggested.

Changes to text: The text has been revised as follows:
Previous text p5, line 116-117: "..the most common physical finding seen in patients with IGM is a painful unilateral subareolar lump"
Revised text p5, line 135-136: "the most common **clinical** finding **on physical examination of** patients with IGM is a **solitary tender palpable lump**".

Comment 2: p5, line 122: 'breast' carcinoma (and elsewhere where carcinoma is

mentioned)

Reply 2: We have modified our text as advised.

Changes to text: We have added the word "breast" before carcinoma in all instances **(see p6, line 142 and p6, line 147.)**

Comment 3: p5 line 128: revise to irregular heterogeneous 'mass' (for BIRADS terminology correctness).

Reply 3: We have modified our text as advised.

Changes to text: We have replaced the word **"lesion"** with **"mass"** **(see p2, line 32; p4, line 97; p4, line 99; p4, line 102; p6, line 148; and Fig 3. description)**.

Comment 4: p5 line 131-134: I do not think it is accurate to suggest that the pathologist needs to be clued into looking for a granulomatous process, this will be obvious to them. The clinical presentation first and foremost needs to be evaluated for infections (much more common) and then exclude less common infectious granulomatous processes like TB; breast CA is usually not a pathologic confounder. Consider removing these statements.

Reply 4: We have modified our text as suggested.

Changes to Text: We have removed the statement previously on page 5 line 131-134: "By indicating on the pathology…core specimen." **(see p6, lines 153-155).**

Comment 5: p5 line 136-137: I do not think this is an accurate conclusion, since immunosuppressives will change the clinical course of any inflammatory process, to include infection. One proposed theory of IGM is pathologically/microbiologically non-diagnosed infection like Corynebacterium or TB, and it has been suggested in relation to the apparent disproportionate prevalence in low-income communities. Autoimmunity is however, the prevailing theory, but not proven by response to immunosuppressive therapy. I would suggest removing this statement, recording or expanding to include other theories.

Reply 5: We have modified the text as advised and chosen to remove the problematic part of the statement which suggests that the prevailing autoimmune theory is due to response to immunosuppressives. We have not elected to expand further at this point as alternative theories, including the proposed theory of IGM being related to infections such as Corynebacterium, have been described in the introduction section **(see p3, line 54-62).**

Changes to text: We have removed the portion of the statement which reads "because of the response to immunosuppressive therapy" **(see page 6 line 158).**

Comment 6: p5 line 142-143: regarding surgical treatment, I would suggest you quote and compare ranges of rates of reported recurrence and complications after surgery alone versus conservative treatment to sustain your discussion. Stating surgery usually does not resolve symptoms is not completely accurate.

Reply 6: Clinical trials directly comparing medication and surgical treatments of IGM are scarce, however, in the article by Pluguez et al, (reference 2), they note that surgical approach may lead to "repeated surgical procedures, increasing the risk of multiple scars." They also quote studies reporting recurrence rates ranging from 13% to 73% after wide surgical excision of IGM masses with "multiple procedures required to achieve complete remission." However, in the largest study to date (77 patients) involving a comparison of medication using steroids (44 patients) versus surgical management (33 patients) of IGM, Yabanoğlu et al, found the recurrence rate to be 20% among the patients who were treated conservatively and 0% in the surgical group after a follow-up period of 16.57 months +/- 18.57 months. The discrepancy in recurrence rates after surgery reported in the literature is large, and it is difficult to directly compare with pharmacological treatment. Therefore, we have decided to remove the statement of concern from the text as it cannot be sustained by literature.

Changes to text: We have removed the statement "…surgical excision does not usually resolve the symptoms and may result in recurrence" **(see p6, lines 165-166**).

Comment 7: p 5, 150: it's unusual to need a repeat biopsy if initial biopsy was a core biopsy, I believe your team had. an unusual scenario; also, most of these patients will have empiric oral antibiotic as the dx of infection would be way more common than IGM particularly in a male patient. I would remove "repeat biopsy", and I would reword to "extended antibiotic therapy"

Reply 7: In our case, repeat biopsy was done because we were not anticipating the result of granulomatous mastitis initially at the time of biopsy. Therefore, cultures for important secondary causes of granulomatous mastitis e.g. TB, were not sent. After discussion with the patient, he agreed to proceed with repeat biopsy to obtain new tissue to send for culture. Since as you pointed out, this may be an atypical scenario, we have modified the text as advised. We have also removed **"surgery"** as an unnecessary intervention, since we have noted earlier in the text that surgery may still be necessary after a diagnosis of IGM if pharmacological therapy fails **(see p6, line 168**).

Changes to test: We have removed "repeat biopsy" and "surgery" from the text.
Revised text p6, line 175: "…avoid **extended antibiotic therapy**."

This change was also made in the Abstract section **(see p2, line 42).**

Comment 8: p6. 152: I would remove "preferred" since there is no guideline or mainstream management strategy for IGM. I would present here (and elsewhere in the manuscript) that this patient got treated as such and report the outcomes. Also, you should specify how the symptoms got better... decreased tenderness, resolution of palpable area, no drainage ...and integrate a time frame to those observations.

Reply 8: We have modified our text as advised and removed "preferred" from both Abstract and Discussion sections. We have also included details of how symptoms improved in the Case Presentation and the Discussion section. Please note that upon further review of our clinic notes, the patient never complained of tenderness. This has been corrected in the text.

Changes to text:

In the Abstract section, we have removed "preferred" and rephrased as follows:
Previous text p2 line 36-37: "Pharmacological therapy initially using corticosteroids followed by methotrexate was the preferred treatment method with good response"
Revised text p2, line 35-36: Our patient was treated pharmacologically, initially using corticosteroids followed by methotrexate, with good response.

In the Case Presentation section, we have deleted **"tender"** from the list of presenting symptoms **(see p3, line74)** and we have added details of how the symptoms improved as follows;
Revised text p5, line 116-122: "The patient was treated with tapering doses of prednisone starting at 50mg to 25mg daily over 4 months. At the 3-month visit (shown in Fig 1b), he was noted to have decreased swelling bilaterally and less drainage from the left peri-areolar sinus tract. He was not able to decrease his dosage below 25 mg of prednisone without reoccurring symptoms. Therefore, he was referred to Rheumatology to start methotrexate. After 6 months of methotrexate at 20mg weekly and slow taper off prednisone, the patient had resolution of swelling and peri-areolar drainage. He has had no further drainage or recurrence of symptoms two years after diagnosis."

In the Discussion section, we have removed "preferred" and have specified how the symptoms got better.
Previous text p6, line152: "…preferred treatment method and demonstrated good symptom control."
Revised text p7, line 177-180: "He was treated conservatively initially using corticosteroids and demonstrated decreased swelling bilaterally and less drainage from the left peri-areolar sinus tract after 3 months, but ultimately achieved symptom resolution after 6 months of methotrexate with weaning off of corticosteroids."

Comment 9: p6, line 153-154: The last statement on this case report should emphasize that this process can occur in male patients, therefore clearly not just parous, child-bearing women can have it. Also, you can restate that your patient had gynecomastia (quantify- mild, moderate..?), which seems to quite possibly allow this patient to experience this rare disease. It would be great if this patient had a prolactin measurement.... since hyperprolactinemic states have been linked to the development of disease in atypical demographics like non-parous females, and can be produced by causes like psych meds, head trauma or brain tumors (all of which can happen in men). Thanks for adding non-smoker to the article.

Reply 9: We have modified the last statement as suggested. Please note that upon further review of our clinical notes, the patient had no formal diagnosis of gynecomastia pre-dating this presentation but rather described a long-standing history of a waxing and waning lump in his left chest. We have modified the text to reflect this.

Changes to text: The last paragraph has been revised as follows:
Revised text p6-7, line 170-176: "Although IGM is usually seen in parous women, it is important for clinicians to be aware of IGM and its presentation in males to be able to correlate typical clinical findings with imaging and biopsy in order to avoid extended antibiotic therapy. Our patient was found to have mild gynecomastia at presentation which may have predisposed him to this rare disease."

Comment 10: Please emphasize and expand on the disease course over follow up with immunosuppressives. Comment on prolactin level, or state that the patient unfortunately did not have that blood test done, but may be relevant.

Reply 10: We have expanded on the disease course and symptoms over follow-up in the Case Presentation Section. Prolactin level was not done as discharge was serosanguinous/purulent discharge from a sinus tract and not milky nipple discharge/galactorrhea. In the Discussion section, we have made note as a limitation that the patient did not have an endocrinological work up, or prolactin level done.

Changes to text: In the Case Presentation section, we have revised the text as follows:
Revised text p5, line 116-122: "The patient was treated with tapering doses of prednisone starting at 50mg to 25mg daily over 4 months. At the 3-month visit (shown in Fig 1b), he was noted to have decreased swelling bilaterally and less drainage from the left peri-areolar sinus tract. He was not able to decrease his dosage below 25 mg of prednisone without reoccurring symptoms. Therefore, he was referred to Rheumatology to start methotrexate. With 6 months of methotrexate at 20mg weekly and slow taper off prednisone, the patient had resolution of swelling and peri-areolar

drainage. He has had no further drainage or recurrence of symptoms two years after diagnosis."

In the Discussion section, we added the following statement:
Revised text p6, line 159-160: "Unfortunately, an endocrinological work up or prolactin level was not performed, which may have been relevant."
Revised text p7, line 177-180: "He was treated conservatively initially using corticosteroids and demonstrated decreased swelling bilaterally and less drainage from the left peri-areolar sinus tract after 3 months, but ultimately achieved symptom resolution after 6 months of methotrexate with weaning off of corticosteroids."

Reviewer D

Comment 1: I don't think it's necessarily true to say the GM should be included in the differential diagnosis (lines 38-40) for male patients. This may be true for certain female patient population, but not really for male patients. I believe that rather than putting it in the differential, it is important to know that the disease exists and be able to correlate imaging with biopsy pathology result to avoid unnecessary surgery by making it discordant. If clinically felt to be infection, the clinicians should try antibiotics first rather than subjecting the patient to unnecessary biopsy trying to exclude this disease from the start.

Reply 1: We have modified our text as suggested and clarified that being aware that the disease entity can occur in males is important to be able to correlate typical clinical findings with imaging and biopsy in order to avoid extended antibiotic therapy. Since surgery may be necessary after a diagnosis of IGM if pharmacological therapy fails, we decided not to list it as an unnecessary intervention following a diagnosis of IGM.

Changes to text:
Abstract Section has been modified as follows;
Previous text p 2, line 38-40: "…to consider IGM in the differential diagnosis of a painful breast mass in a male patient in order to provide appropriate treatment and avoid unnecessary antibiotic therapy or surgery."
Revised text p2, line 39-42: "… to be able to correlate typical clinical findings with imaging and biopsy in order to avoid extended antibiotic therapy."

Comment 2: Lines 46-49. The conditions listed are some of the theories and are not something that "must be excluded before a diagnosis of GM is made." More literature search is suggested on this statement.

Reply 2: We wanted to clarify that the conditions listed are thought to be secondary causes of granulomatous mastitis and all of these entities must be excluded before a

diagnosis of **idiopathic granulomatous mastitis (IGM) is made.** According to literature review we conducted for theories around the development of IGM, one proposed theory is pathologically/microbiologically non-diagnosed infection like Corynebacterium or TB, or an autoimmune process, which is the prevailing theory.

Changes to text: None

Comment 3: Lines 81-82. Would change to cortical thickening instead of thickened left axillary lymph node. 0.3 cm cortical thickness is normal. Sometimes it may be considered suspicious if it is strikingly asymmetric or only single node that is different. Was this the case?

Reply 3: The left axillary lymph nodes were asymmetrically prominent compared to the right- although within normal limits. The asymmetry raised some suspicion and prompted FNA investigation. We have modified the text in the Case Presentation section as well as the Figure 3 description as suggested to" cortical thickening" instead of "thickened left axillary lymph nodes."

Changes to text 3:
We have modified the text as advised in the Case presentation section:
Previous text p4, line 81-82: "There were multiple mildly thickened left axillary lymph nodes with cortex measuring up to 0.3 cm."
Revised text p4, line 88-90: "Multiple left axillary lymph nodes were asymmetrically prominent compared to the right but demonstrated cortical thickening within normal limits (shown in Fig. 3d)."

Comment 4: Fig 2. Would put arrow on the right breast finding.

Reply 4: We have added an arrow to the right breast finding as suggested.

Changes to text: See revised Figure 2. The figure description has also been modified to include "(white arrow)" after right breast findings **(see p9, Figure 2)**.

Comment 5: Fig 3 D. The cortex that is the thickest actually appears to be the inferior portion unless that is just the orientation of the probe that makes it artificially thicker. If that were the case, state so or use a different image.

Reply 5: We The inferior portion of the node is indeed the thickest (right side of image). Unfortunately, we do not have another image of the lymph node, but we have removed the marker and kept the image to demonstrate that the lymph node was normal in appearance. The measurement has also been removed from the text.

Changes to text: Please **see revised Figure 3D** with marker previously in the mid/superior aspect removed.
Revised text p4, line 88-90: "Multiple left axillary lymph nodes were asymmetrically prominent compared to the right but demonstrated cortical thickening within normal limits (shown in Fig. 3d)."
Revised figure 3D description p9: "left axilla revealed multiple prominent lymph nodes with cortical thickening measuring up to 0.3 cm (measurement not shown).

Comment 6: Fig 3 F. There is extra E on the image. Also, consider putting an arrow on the cystic portion to point that out for the readers.

Reply 6: Thank you for pointing this out, our version does not have an extra E on the image. We have resubmitted the image as we have it, without an E. We have also added an arrow to the cystic portion of the mass on Figure 3F.

Changes to text: **See p9, Figure 3F** description has been modified to include "(white arrow)" after the description of the cystic spaces to point that out to the readers.

Comment 7: Fig 4. Please include more description about the slide with arrows to point to the findings.

Reply 7: Unfortunately, the images are not in high enough magnification to put arrows but we have encircled the main findings.

Changes to text: Please see revised Figure 4.
The legend description for this figure has been modified as follows:
Revised Figure 4, p9: "Histologic images of idiopathic granulomatous mastitis in a 46-year-old male patient. Right breast core needle biopsy on initial presentation **(A)** and on repeat biopsy **(B),** both revealed necrotizing granulomatous mastitis, circled in red (Hematoxylin and eosin, 8X magnification)."

Comment 8: Lines 125-126. It says imaging is useful but the next sentence is contradictory. Imaging is nonspecific for GM.

Reply 8: We have removed the statement indicating "useful investigations" as this does present a contradiction. These investigations are instead a necessary part of the work-up although non-specific for IGM

Changes to text: We have removed the sentence "Useful investigations for diagnosis of IGM include mammography and ultrasound." The paragraph now begins with "On mammographic examination…" **(see page 6, line 145).**

Comment 9: Lines 148-151. Same comment as #1.

Reply 9: We have modified the last paragraph of the Discussion section as advised.

Changes to text: In the discussion section, we have changed the text as follows;
Previous text p6, line 148-151: Although IGM is usually seen in women, it is important for clinicians to consider IGM in the differential diagnosis of a male patient presenting with a painful breast mass. In doing so, more targeted pathological and diagnostic evaluations can be made and patients can avoid repeat biopsy, unnecessary antibiotic therapy or surgery.
Revised text p6-7, lines 170-175: Although IGM is usually seen in parous women, it is important for clinicians to be aware of IGM and its presentation in males to be able to correlate typical clinical findings with imaging and biopsy in order to avoid extended antibiotic therapy."