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Peer Review File

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**Reviewer A**

Comment 1: An interesting and rare case, well documented and discussed.
**Reply 1: We appreciate your review and comments.**

**Reviewer B**

This study aimed to report the first case of GG complicated by breast necrosis in the setting of active COVID-19 infection and to discuss the potential role of COVID-19 infection in this rare complication. This case report is very interesting and rather unique. I think it will be interesting for the Journal's readers. I have some suggestions:

Comment 1: Introduction: "GG is a rare condition of unknown etiology characterized by rapidly enlarging breast tissue to greater than 1.5kg in the peripartum setting" – some authors define gigantomastia as an enlargement of breast, where more than 1500 g of breast tissue needs to be removed from the breast, some as the weight of the breasts estimated to be 1500 g, some base the diagnosis only on physical symptoms (which seem to be more logic) (Dancey A, Khan M, Dawson J. Gigantomastia a classification and review of the literature. J Plast Reconstr Aesthet Surg. 2008;61:493–502), in case of GG – I think the most common "definition" include "rapid and disproportionate enlargement of the breasts during pregnancy" ("a fast and excessive growth of the breasts in pregnant women") with less focus on the weight – I think you should specify the definition you cited…

**Reply 1: We chose to include the quantitative definition of gigantomastia due to the tangible nature of this definition [1]. However, we acknowledge that most sources we referenced describe a clinical definition for gestational gigantomastia [2-4], as is consistent with the source you provided. This is consistent with how we diagnosed the patient, so we have changed the manuscript accordingly.**

**Changes in the text: Line 35-36 previously defined GG as "characterized by rapidly enlarging breast tissue to greater than 1.5kg in the peripartum setting" and was changed to "characterized by rapid and significant enlargement of the breast tissue in the peripartum setting."**

Comment 2: Some more information on the case is needed: patients characteristics before pregnancy (BMI, breast size), before delivery (weight gain, breast enlargement), details concerning her therapy (how long did she take drugs, dosages), when the condition subsided?, how long is the follow-up, also please provide details about the child (weight, sex), was she breastfeeding for these first two postpartum days?

**The patient's baseline BMI was 28.12 and at the time of delivery the patient's weight was 184lbs with a BMI of 33.7. Though the patient's exact breast size at baseline is unknown, the patient had discussed breast reduction with a primary care provider three years prior due to back pain secondary to large breast size. Because the patient did not regularly see an obstetrician during her pregnancy, the timeline of breast enlargement was not documented, but the patient did not endorse concern for breast pain or enlargement until postpartum day 3. The patient did not attempt breastfeeding in the first two postpartum days before representing for breast pain. While hospitalized, the patient attempted breast pumping briefly for pain relief. Medications given to suppress lactation were cabergoline 0.25mg BID for two day, then changed to bromocriptine 2.5mg QD for 60 days. Unfortunately, the patient was lost to follow up despite multiple attempts at contact by the care navigator team. The patient gave birth to a female infant weighing 2140g born at 33 weeks 5 days due to preterm premature rupture of membranes.**

**Changes in the text:**
**The sentence was added to line 49 "The patient had a body mass index (BMI) of 33.7 at the time of presentation, from a pre-pregnancy BMI of 28.12."**

**Line 55 was changed from "delivered a healthy baby" to "delivered a healthy female infant"**

**The following sentence was added to line 65: "The patient did not raise concern for breast enlargement prior to giving birth."**

**The following line was added: "Though the patient's breast size prior to pregnancy was unknown, the patient had raised concern for back pain due to large breast size at a past wellness visit." See line 66-67.**

**The following sentences were added to lines 81-83: "She was ultimately diagnosed with GG and started on bromocriptine 2.5 mg QD for 60 days for lactation suppression. The patient did not attempt breast feeding prior to**

**admission, but used a breast pump briefly during admission with partial resolution of chest pain."**

**To address questions related to follow up, it is not noted in the discussion on line 152 that there was "loss to follow-up."**

Comment 3: are Covid-19 positive patients given enoxaparine routinely after delivery? I understood that your patient did not receive heparin although she was mildly symptomatic for Covid-19 -please discuss this in reference to current literature
**Reply 3: The possibility of thrombosis secondary to COVID-19 infection in the peripartum setting inspired international guidelines for thromboprophylaxis in infected peripartum patients at the time of this patient's delivery and hospitalization [5-7]. Our patient was started initially on therapeutic anticoagulation but the decision was made to discontinue it per multidisciplinary discussion after septic thrombosis was ruled out. The most recent guidelines on thromboprophylaxis and COVID 19 published by the NIH in 2022 moderately recommend thromboprophylaxis in pregnant women but do not give specific recommendations for postpartum women [8].**

**Changes in the text:**
**A short paragraph was added to address further workup and treatment of a possible underlying hypercoagulable syndrome in a peripartum patient with COVID-19 infection. Lines 144-147 read "While there was limited evidence to support use of thromboprophylaxis in hospitalized patients with COVID-19 infection at the time our patient presented, newer guidelines strongly recommend thromboprophylaxis in non-pregnant infected patients (15). There are no recommendations specific for postpartum women (15-16)."**

Comment 4: You suggest that this condition was related to hypercoagulation due to Covid-19 and you stopped anticoagulation (what kind of anticoagulant you administered?) before patient's discharge /a few days after/?
**Reply 4: The patient was initiated on therapeutic enoxaparin, but anticoagulation was intermittently refused by the patient, and stopped by the primary obstetrics team.**
**Changes in the text:**
**Line 79-80 previously read "Tissue and blood cultures remained negative, and antibiotics and anticoagulation were discontinued," and has now been changed to "Tissue and blood cultures remained negative, and antibiotics were discontinued. Anticoagulation was refused by the patient and later discontinued after multidisciplinary discussion."**

Comment 5: Please provide more (and better…) photographs showing patient's chest just after delivery (if available), with GG, and after treatment (her "normal" breasts?)
**Reply 5: We do not have other photographs to provide, due to the patient being lost to follow up. The picture included is the only picture available.**
**Changes in the text: This is addressed by the addition of "loss to follow-up" to line 152.**

**Reviewer C**

Comment 1: Would include a comment on lactation attempts if there were any. Was breastfeeding attempted? Did the patient hand express or pump to relieve pressure?
**Reply 1: The patient did not breastfeed in the first two postpartum days. A breast pump was used briefly during admission with partial resolution of chest pain. However, breast pump use was stopped in an effort to decrease long term lactation, and the patient was started on bromocriptine.**
**Changes in the text: The sentence was added to line 83: "The patient did not attempt breast feeding prior to admission but used a breast pump briefly during admission with partial resolution of chest pain."**

Comment 2: Did mastitis play a contributory role? Did the breast erythema improve with initial antibiotic treatment?
**Reply 2: Mastitis did not play a role in this patient's case. Mastitis was considered in the differential diagnosis, and can cause symptoms similar to those seen in both gestational gigantomastia and COVID-19 [9]. However, on exam, the magnitude of breast enlargement was much more significant relative to the erythema present. Additionally, the lack of tenderness to palpation or lymphadenopathy suggested an etiology other than mastitis.**
**Changes in the text: None**

Comment 3: Please include picture of the pathology of breast biopsy, showing the infarctive necrosis.
**Reply 3: We have included an image of the pathology of the breast biopsy demonstrating infarctive necrosis and rare thrombosed blood vessels.**
**Changes in the text: Figure 4.**

Comment 4: Is there any follow up and/or follow up imaging available for this patient? Was a hypercoagulable workup done?

**Reply 4: This patient was lost to follow up despite multiple attempts at contact by the care navigator team. Therefore we do not have follow up imaging or hypercoagulability workup available.**

**Guidelines at the time of this case endorsed obtaining coagulation labs, specifically including platelet count, activated partial thromboplastin time (APTT), partial thromboplastin time (PT), fibrinogen, and d-dimer, for any peripartum patient hospitalized with COVID-19 infection[6-7]. New literature warns against interpretation of the above labs in the peripartum population with COVID-19, where overlap between expected laboratory changes associated with pregnancy and abnormal changes due to COVID-19 can make clinical interpretation difficult [6-7].**

**With that being said, our patient's biopsy demonstrated a very unusual pattern of small vessel thrombosis, so a full hypercoagulability workup may be helpful in detecting other underlying hypercoagulable syndromes. More specific laboratory tests for common thromboembolic diseases are warranted if a coagulation panel and antiphospholipid antibody testing are unrevealing [10]. However, peripartum pathophysiology and active thrombosis can affect the results of both a coagulation panel and tests for common thrombophilias [11]. Specifically, increases in fibrinogen and coagulation factors alter coagulation parameters, and antiphospholipid antibodies are found in in up to 2.2% of obstetric patients [11]. Tests ideally would need to have been performed 6-12 months after her initial presentation [11]. At follow-up, we would have considered repeating coagulation labs and testing for antiphospholipid antibodies after a period of 6-12 weeks. If these labs normalized, we would consider adding specific tests for genetic mutations [10-11]. The most common inherited thrombophilia is factor V Leiden [10-11]. Though inherited thrombophilias are unlikely to cause thrombosis alone in low-risk patients, post-partum women are in a high-risk state, especially those admitted to the hospital [11]. Additionally, certain acquired thrombophilias, specifically antiphospholipid syndrome and prothrombin gene mutations, are particularly high-risk for thrombosis in pregnancy [11].**

**Changes in the text:**
**Lines 148-151 now reads "Furthermore, a repeat coagulation panel followed by testing for common inherited and acquired hypercoagulability syndromes might have been considered (17-18). However, these would have needed to be performed 6-12 weeks after discharge as the peripartum state and active thrombosis can affect these laboratory results (17-18)."**

Comment 5: Line 36 – add ethnicity of the patient if known
**Reply 5: The patient's ethnicity has been added, see changes in the text.**

**Changes in the text: Line 44 previously "18-year-old woman…" now "18-year-old black woman…"**

Comment 6: Line 38 – as definition of "fully vaccinated" appears to be changing soon, please specify the type of vaccine and the number of doses received, also the timeline of when vaccination occurred before onset of symptoms
**Reply 6: The patient received two doses of the COVID-19 vaccine as was medically indicated at the time given that this this event occurred prior to the initiation of booster vaccinations.**
**Changes in the text: Line 46-47 previously "despite being fully vaccinated" now "despite being fully vaccinated for COVID-19 according to vaccination guidelines at the time of presentation."**

Comment 7: Line 48 – please specify antibiotic regimen
**Reply 7: The antibiotic treatment during hospitalization included vancomycin/piperacillin/tazobactam initially. The antibiotic regimen was subsequently narrowed to ampicillin/sulbactam.**
**Changes in the text: Line 59-61 was changed from "she was started on empiric broad spectrum antibiotics" to "she was started on empiric broad spectrum antibiotics consisting of vancomycin/piperacillin/tazobactam and subsequently narrowed to treatment with ampicillin/sulbactam."**

Comment 8: Line 51 – Is the previous breast size known?
**Reply 8: Exact breast size prior to pregnancy is unknown; however, three years prior to pregnancy the patient did discuss the possibility of breast reduction dues to breast size and resultant back pain at a pre-employment physical exam.**
**Changes in the text: The following line was added: "Though the patient's breast size prior to pregnancy was unknown, the patient had raised concern for back pain due to large breast size at a past wellness visit." See line 67.**

Comment 9: Line 54 – was the bedside core biopsy targeting any particular lesion? Was ultrasound used?
**Reply 9: The bedside core biopsy targeted one of the palpable lesions that corresponded to one of the hypoechoic nodules seen on diagnostic ultrasound. Ultrasound guidance was not used.**

**Changes in the text: Lines 71-72, sentence ending in "core needle biopsy" now ending with "targeting a palpable lesion which corresponded to one of the hypoechoic nodules seen on diagnostic ultrasound."**

Comment 10: Line 59 – the rationale for the septic pelvic thrombophlebitis is not clear to me. Did she have symptoms?
**Reply 10: The primary obstetrics team was concerned for septic pelvic thrombophlebitis based on the patient's persistent fevers despite continuous antibiotic use status-post dilation and curettage performed for concern for retained products of conception.**
**Changes in the text: Line 76-79 now reads "She was started on therapeutic anticoagulation due to concern for septic pelvic thrombophlebitis in the setting of persistent fever after dilation and curettage performed for concern for retained products of conception."**

Comment 11: Line 102 – Breastfeeding may not necessarily be possible after breast reduction
**Reply 11: Retrospective studies and meta-analyses have demonstrated some cases of reduced success with breastfeeding after breast reduction surgery, largely dependent on subareolar parenchymal structure preservation during surgery [12-13]. This is one reason that medical and conservative management is preferred to surgical treatment of gestational gigantomastia. According to two meta-analyses, compromised breast feeding was not demonstrated in cases of preserved subareolar parenchyma, according to two meta-analyses, which supports an attempt at partial mammoplasty prior to complete mammoplasty in young mothers [12-13].**
**Changes in the text: To lines 137-140, we have added the sentence "Partial mammoplasty can compromise lactation depending on the degree of preservation of subareolar parenchymal structure, and conservative and medical management remains the preferred first step (13-14)."**

**Reviewer D**
Comment 1:
The authors describe a case report of Gestational Gigantomastia (GG) in an 18 year old female following her first pregnancy. While a rare condition there are several reports in the literature including a systematic review of 50 case reports already published. The case report and the acute events described within are difficult to follow as written. It appears that the patient suffered from a combination of pathologies but how they play into each other is not clearly elucidated. The patient's demographics/ prior health conditions/perinatal course are not discussed and their relation to the

patient's presenting pathologies. In particular it would appear that the process had occurred before she gave birth which is the usual presentation of this condition. They postulate that in this patient the GG was triggered by her hypercoagulable state that was due to her COVID 19 infection +/- pelvic sepsis but antibiotics and anticoagulation was stopped before the patient was discharged. They describe infarctive necrosis as a 'new' addition to the literature on GG but do not explain why this differs from fat/skin necrosis commonly described in this condition or give any details of the long term outcome for this patient and any subsequent sequlae/ implications for management of other patients.

The authors therefore, have not added any new aspects to this body of literature.

**Reply 1: We appreciate the reviewer's comments. We appreciate that the reviewer points out the benefit of adding the patient's demographic information and prior health history to help elucidate how this played into her pathology. This patient did not have a significant health history nor a complicated perinatal course. The unique finding of infarctive necrosis of the breast tissue is a new pathologic finding of gigantomastia not yet described in the literature. The characteristic histology of gestational gigantomastia shows hypertrophy of the normal lobules and ducts of the breast, similar to physiologic changes of pregnancy, as described in lines 92-94 of our manuscript [2-3]. There is occasional stromal fibrosis, lymphocytic infiltration, and/or vascular proliferation noted [2-3]. In contrast, breast tissue infarctive necrosis has not been described in patients with gestational gigantomastia.**

**Gross skin necrosis has been described in gestational gigantomastia [2-3]. This is different from infarctive necrosis of the breast tissue. Gross skin necrosis generally forms large ulcers rather than the microscopic necrotic changes seen in the breast tissue biopsy of our patient. Gross skin necrosis is caused by the rapid growth of breast tissue and angiogenesis within the breast disproportionate to the rate of growth of the skin, rather than small vessel thrombosis which caused the infarctive necrosis seen in our patient [2]. The infarctive necrosis observed in our patient is also distinct from fat necrosis. Fat necrosis is caused by hemorrhage in fat tissue due to extrinsic forces such as trauma or surgery [14]. Furthermore, fat necrosis typically appears as calcifications and commonly forms cystic structures [14]. This was not seen in on ultrasound of our patient. We appreciate the comparison of infarctive necrosis to other common breast histologies, including skin necrosis and fat necrosis. We agree that a comparison of these distinct histologic entities would add to our discussion.**

**The aim of our case report is to describe a new histologic finding not yet described in gestational gigantomastia in the setting of the novel COVID19 infection. We agree and by no means sought to suggest that a hypercoagulable state caused by COVID19 infection was the cause of her gestational gigantomastia. Rather, our discussion explores the possible interaction between COVID19 and the infarctive necrosis observed in this case. We feel that this is a valuable finding to report due to the lack of literature on COVID19 in the peripartum patients with gestational gigantomastia.**

**While our patient was lost to outpatient follow-up, her hospital course required a prolonged inpatient stay for workup and pain typical of gestational gigantomastia. However, she did not decompensate due to COVID19 or her gestational gigantomastia. This supports our conclusions recommending a stepwise treatment approach beginning with conservative treatment measures. We have added these details to our description of the case.**

**Overall, we appreciate Reviewer D's analysis of our manuscript, and seek to make changes which address these comments, as delineated below.**

**Changes in the text:**
**Line 44 previously "18-year-old woman…" now "18-year-old black woman…"**

**To differentiate between fat necrosis and infarctive necrosis, lines 106-108 now read "Fat necrosis is caused by hemorrhage in fat tissue, usually due to trauma or surgery, and typically results in gross calcifications and cystic structures in the breast (8). In contrast, the infarctive necrosis seen in our patient demonstrated small vessel thrombosis." To contrast skin necrosis with infarctive necrosis, lines 101-104 now read "Gross skin necrosis has been reported in GG (1). Gross skin necrosis forms large ulcers caused by the rapid growth of breast tissue and angiogenesis within the breast disproportionate to the rate of growth of the skin, rather than the small vessel thrombosis causing the infarctive necrosis in our patient (2)."**

**The patient's long-term outcomes are now addressed by line 79 reading "Over the next two to three days her breast pain and swelling improved with conservative measures. The patient did not require intensive care for COVID19 infection." Lines 148-151 now reads "Furthermore, testing for common inherited and acquired hypercoagulability syndromes might have been considered, but these would have needed to be performed 6-12 weeks after discharge as the**

**peripartum state and active thrombosis can affect these laboratory results (17-18).”**