Peer Review File

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Reviewer A

Comment 1: Addition of incidence/prevalence of Ehler-Danlos Syndrome in community and more specifically what percentage of them have hEDS subtype.

Reply 1: Thank you for taking the time to review our article. As per your recommendation, we have included information on the incidence of Ehler-Danlos and the hEDS subtype in the INTRODUCTION section.

Changes in the text 1: Within the INTRODUCTION, see (Page 3, lines 58-59) and (Page 3, lines 64-65).

Comment 2: The report is written in a way, it looks very repetitive and also in some areas it seems to cater to a medical student/basic level audience only (eg; lines 160-167). I think should be tidied up.

Reply 2: Thank you for this feedback. We have modified text throughout the case report to reduce repetitive phrasing and cater to a more advanced readership.

Changes in the text 2: See CASE PRESENTATION (Page 4, lines 106-109), see DISCUSSION (Page 6, lines 142-145), see DISCUSSION (Page 6, lines 162-164), and see DISCUSSION (Page 7, lines 175-182).

Reviewer B

Comment 1: Authors did not show the detail of Goldilocks mastectomy which they selected to prevent EDS-associated poor wound healing due to radiation therapy. Author should show the picture of the preoperative skin condition, and preoperative design to perform Goldilocks mastectomy, intraoperative findings, and postoperative them.

Reply 1: We thank the reviewer for performing a thorough analysis of our study and providing these useful suggestions. We agree that adding photographs of the patient's preoperative skin condition, preoperative design, intraoperative findings, and postoperative result would add great value to the case report. While we took a postoperative photograph following Goldilocks mastectomy and are eager to include this photograph, unfortunately we did not take any preoperative or intraoperative photographs at the time. We regret the omission of preoperative and intraoperative photographs. However, beyond providing a postoperative photograph, we have also added text describing our Goldilocks mastectomy procedure to provide greater clarification on the selected breast reconstruction option.

Changes in the text 1: See (Page 4, lines 94-97), see Figure 3, and see Figure 3 legend (Page 12, line 317).

Comment 2: The biggest defect of this article is to lack in the pictures during and post radiation therapy.

Reply 2: We are grateful for the reviewer's close read and thoughtful feedback. We

agree that patient photographs taken during and post radiation therapy would provide greater strength to this case report. Unfortunately, our care team was not able to take photographs of the patient's skin during and after radiation therapy out of deference to the patient's preference to avoid skin photography. Although we regretfully are unable to provide radiation therapy photographs, we have added further text clarifying the patient's skin changes that occurred during and after radiation therapy.
Changes in the text 2: See CASE PRESENTATION (Page 5, lines 122-125).

Comment 3: Author should submit this article only after several years whether their selection of the combination of Goldilocks mastectomy and radiation therapy would be adequate for not only local condition but also disease-free survival.
Reply 3: Once again, we thank you for this valuable feedback. We agree that greater passage of time would provide increased value in terms of presenting long-term patient outcomes regarding selection of Goldilocks mastectomy and radiation therapy. Our patient underwent mastectomy and radiation therapy five years ago, and as of her latest clinic visit in 2021, she remains free of local, regional, and distant cancer recurrence. We believe that a five-year period following mastectomy/radiation therapy initiation provides significant value to clinicians. We have clarified language in the case report to reflect the patient's latest clinic date.
Changes in the text 3: See ABSTRACT (Page 2, lines 40-41), CASE PRESENTATION (Page 5, lines 122-127), CASE PRESENTATION (Page 5, lines 135-136), and DISCUSSION (Page 8, lines 209-211).

Reviewer C
Comment 1: The case report is well-written, however the significance of the report is unclear. One major limitation is that no long-term outcomes are presented.
Reply 1: We thank the reviewer for this valuable feedback. We appreciate this comment and agree that inclusion of long-term outcomes would provide greater significance to this case report. We have altered the text to include long-term outcomes in response to surgical management, radiation therapy, and disease recurrence.
Changes in the text 1: See ABSTRACT (Page 2, lines 40-41), CASE PRESENTATION (Page 5, lines 122-127), CASE PRESENTATION (Page 5, lines 135-136), and DISCUSSION (Page 8, lines 209-211). We have also modified language to emphasize our focus on long-term outcomes – see ABSTRACT (Page 2, line 30 & line 46)

Comment 2: Adjuvant therapies, including the 4 to 6 week delay to radiation therapy, are mentioned, but no subsequent clinic follow up appointments after adjuvant treatments are brought up.
Reply 2: We greatly appreciate the reviewer's feedback. We agree that follow-up

information regarding adjuvant radiation and endocrine therapy would add greater value to this case report. To this end, we have included specific follow-up details on our patient's treatment course; overall, our patient endured minimal side effects.
Changes in the text 2: See ABSTRACT (Page 2, lines 40-41), CASE PRESENTATION (Page 5, lines 122-127), CASE PRESENTATION (Page 5, lies 135-136), and DISCUSSION (Page 8, lines 209-211).

Comment 3: Given the extensive discussion regarding wound healing in the context of Ehlers-Danlos, a picture of the wound would be of interest.
Reply 3: We thank the reviewer for this important feedback. We agree that an image of the wound would strengthen our case report. Unfortunately, our care team was unable to obtain wound photographs during or after radiation therapy out of deference to the patient's preference to avoid skin photography. To provide more context, we have included a postoperative photograph of the overall Goldilocks mastectomy design & additional sentences describing the technique we used to perform Goldilocks mastectomy reconstruction. Additionally, we have included a detailed description of the minor skin reaction endured at the onset of radiation therapy.
Changes in the text 3: See CASE PRESENTATION (Page 4, lines 94-97), see Figure 3, and see Figure 3 legend (Page 12, line 317). Also see CASE PRESENTATION (Page 5, lines 122-125).

Comment 4: Similarly, the date at which the patient was most recently identified in clinic to have no evidence of recurrence of disease would be useful. And whether she initiated the adjuvant endocrine therapy that was recommended and whether she tolerated it for the prescribed duration. Without such follow up data points, the report has limited utility for future reviews of the literature. While the considerations for this combination of diseases are described, without outcomes data it is unclear whether there is evidence to support the authors' final decisions regarding management.
Reply 4: We are grateful for this valuable feedback. We agree that without specific follow-up clinic visit dates, details on long-term disease recurrence, and adjuvant therapy follow-up, our case report does not provide significant value to practicing clinicians. To this end, we have carefully combed through our patient records, and updated the case report accordingly to include details about the patient's latest clinic follow-up date, data about the patient's disease recurrence status, and information about the patient's response to adjuvant endocrine therapy.
Changes in the text 4: See ABSTRACT (Page 2, lines 40-41), CASE PRESENTATION (Page 5, lines 126-127), CASE PRESENTATION (Page 5, lines 135-136), and DISCUSSION (Page 8, lines 209-211).

Comment 5: Even with the above changes the report would be of questionable utility. What would perhaps make for a more useful manuscript would be a case

series that is not limited to Ehlers-Danlos syndrome but to connective tissue disorders in general. If the authors have access to a cancer registry at their institutions, they may be able to identify additional patients who have connective tissue disorders using the free text portions of the registry, in which case they would likely have access to longer term outcomes data and could discuss the results of the particular management plans selected for each patient. This would be of much greater use to the clinician and clinical researcher. Or, depending on the extent of literature that already exists for patients with connective tissue disorders in breast cancer, they could write a review of the literature for this topic.
Reply 5: We thank the reviewer for the valuable and insightful feedback. We agree that a broader case series focused on cancer management in patients with connective tissue disorders would be of significance to practicing clinicians and clinician-scientists. Furthermore, we agree that a literature review of breast cancer management in patients with connective tissue disease also be of great significance to oncology literature. Unfortunately we do not have easy access to a broad cancer registry at our institution, and are thus unable to perform a review of institution-wide cancer management in patients with connective tissue disorders.

Although the reviewer suggests that the present case report may not hold significant value for clinicians, we would like to emphasize why this case report is important.

Very few papers exist on breast cancer management in patients with connective tissue disorders (Chin et al. and Shuck et al.), and these existing papers cover systemic autoimmune connective tissue disorders. There is currently a literature gap on breast cancer management principles in individuals with inherited, collagen-related connective tissue disorders. As a result, there are no definitive guidelines on how to manage the medical, surgical, and radiation therapy aspects of breast cancer in patients with inherited, collagen-related connective tissue disorders such as Ehlers-Danlos syndrome. This was a significant issue that our institution encountered while caring for our patient with breast cancer and Ehlers-Danlos syndrome. Because of the lack of guidelines governing medical, surgical, and radiation therapy care, our medical team had to make various clinical decisions with best practice knowledge instead of evidence-based knowledge. Our case report is of significance to practicing clinicians because it provides long-term outcomes for our patient following Goldilocks mastectomy, adjuvant radiation therapy, and adjuvant endocrine therapy, and because as of the patient's latest clinic follow-up visit, she remains free of local, regional, and distant disease. We believe our case report may help guide future clinicians who manage cancer in patients with inherited, collagen-related connective tissue diseases like Ehlers-Danlos syndrome, and we hope our case report spurs further research and associated clinical guidelines. We have added additional text in the case report to emphasize the unique angles it provides.

Chin KY, Chalmers CR, Bryson AV, Weiler-Mithoff EM. Breast reconstruction in the high risk patient with systemic connective tissue disease: a case series. *J Plast Reconstr Aesthet Surg*. 2013;66(1):61-66. doi:10.1016/j.bjps.2012.07.024

Shuck J, Patel KM, Franklin B, Fan KL, Hannan L, Nahabedian MY. Impact of Connective Tissue Disease on Oncologic Breast Surgery and Reconstruction. *Ann Plast Surg*. 2016;76(6):635-639. doi:10.1097/SAP.0000000000000265

Changes in the text 5: See DISCUSSION (Page 7, lines 179-180), DISCUSSION (Page 8, lines 209-214), and CONCLUSION (Page 9, lines 227-229).

Reviewer D

Comment 1: The authors have not stated whether the opposite breast was reduced – the patient will remain with considerable asymmetry despite a Goldilocks procedure; a conventional mastectomy with an external prosthesis that fits comfortably on a flat chest wall might be preferable.

Reply 1: We thank the reviewer for this insightful feedback. We agree that the case report would be strengthened by including this detail. As per patient preference, the opposite breast was not reduced. We have added text in the case report to reflect this.

Changes in the text 1: See CASE PRESENTATION (Page 4, line 97).

Comment 2: Heart spare techniques are not mentioned – these can help displace the heart inferiorly so the anterior descending coronary artery no longer lies in the radiation field.

Reply 2: We are grateful to the reviewer for this valuable feedback. In the original submitted paper, we had actually mentioned the use of heart spare techniques. We highlight these sentences below.

Changes in the text 2: See CASE PRESENTATION (Page 4, lines 107-108), and CASE PRESENTATION (Page 5, lines 119-121).

Comment 3: The authors might like to comment on whether a diagnosis of EDS would influence the decision for upfront chemotherapy in a phenotype appropriate patient – triple negative cancer or HER2 positive. They have stated that neoadjuvant chemotherapy (NACT) was not chosen in this case because of the poor chemosensitivity of this biological subtype (ER/PR positive; HER2 negative) coupled with cardiotoxicity concerns – but the latter would also apply to adjuvant chemotherapy which this patient is likely to receive. Does EDS per se influence the primary treatment decision? NACT can downstage disease and lead to de-escalation of surgery that may be beneficial for EDS patients (e.g. conventional lumpectomy after complete response to NACT with targeted axillary dissection).

Reply 3: We thank the reviewer for this important feedback. We agree that including information on whether diagnosis of EDS can impact the decision for upfront chemotherapy would add significant value to this case report. We confirm

that our patient did not receive either neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy (ACT). As described above, the patient did not receive NACT due to the patient's significant cardiac comorbidities & poor cancer chemosensitivity. However, the patient also did not receive ACT due to significant cardiac comorbidities & a low oncotype score of 19. Although our specific patient did not qualify for NACT or ACT, we acknowledge that diagnosis of EDS by itself is not a contraindication for NACT or ACT. We have added text in the case report to reflect this.

Changes in the text 3: See CASE PRESENTATION (Page 5, lines 127-134).