Peer Review File

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Reviewer A

It gives me pleasure to review the manuscript titled "Management of a decade-old recurrent chylothorax with breast fistulization". The authors described a patient with recurrent chylothorax which was treated successfully after surgery. This case highlights the need for multidisciplinary care and detailed anatomical evaluation for refractory chylothorax. It is more desirable if more description can be made on the search for aetiology, and correlate the initial rib biopsy and subsequent occurrence of chylothorax. Here are my comments to the authors:

Major comments:

1. It is uncommon to encounter fistulization due to chronic pleural effusion or chylothorax in non-operative conditions. Instead, chronic infection (esp tuberculous pleuritis) or repeated pleural intervention leading to an unhealed subcutaneous tract should be considered. Did the patient receive repeated instrumentation through the chest wall between 2013 and 2019?

   Response: Thank you for this question. It is difficult to discern as we do not have records from the patient's outside facilities. Per the patient, she received some thoracenteses, but not on a routine basis and intermittently. Therefore, we conclude that an unhealed fistula is the most likely scenario. We sent pleural fluid for microbial analysis and it was unremarkable.

   Changes: Added line regarding microbial analysis, lines 82-84

2. During the surgery, were biopsies taken of the sinus tract and pleural tissue?

   Response: Thank you for this question. No, biopsies were not taken.

   Changes: None

3. Thoracic duct embolization is not without complication. The authors may highlight several important complications of TD embolization in the discussion session.

   Response: We agree with the reviewers comments and will add accordingly.

   Changes: Added complications, lines 158-160

4. Line 15. Please use “non-traumatic” instead of “atraumatic” to maintain the consistency

   Response: We agree with the reviewers comments and will add accordingly.

   Changes: Non-traumatic, line 15

5. Lines 59 and 60. Was any cause found to explain the chronic back pain and shortness of breath, which happened before the onset of pleural effusion?

   Response: Thank you for your question. Upon review of the records, there was no attributable source that could be correlated to the patients dyspnea and chronic back pain.

   Changes: None

6. Line 63. Were any pleural fluid analysis results, particularly fluid triglyceride and cholesterol levels, bacterial and mycobacterial culture, available? Similarly, were results available in subsequent workup (line 79)?

   Response: Although we do not have the initial pleural fluid analysis, the patient describes a milky fluid which is corroborated by notation from outside providers. Necessary changes have been made to the manuscript.

   Changes: Added pleural fluid analysis, lines 82-84

7. Line 63. When did the chylous pleural effusion first occurred? Was it happen right after the chest tube insertion for pneumothorax, or months afterwards?

   Response: Thank you for your question. Due to lack of access to outside documentation, we were unable to determine the initial onset of chylothorax. However, the patient states this was noticed at the time of initial chest tube placement.

   Changes: None

8. Line 66. Where was the exact leakage point? How did the chyle go into the pleural space? Was there an associated venous obstruction near the entry point of the right lymphatic duct into the venous system?

   Response: There were diffuse communications between the right sided thoracic duct/paraspinal lymphatics and right medial pleural space spanning T3-11. No venous obstruction was identified.

   Changes: Added thoracic levels, line 85

9. Line 77. Chyle is not generally believed to be an irritant and is unlikely to induce pleural thickening. Was there an additional pathology? Was a pleural biopsy taken? Could it be

pseudochylothorax that can induce pleural thickening and chylous appearance (although you have confirmed the chyle leakage)?

Response: Thank you for your thoughtful response. Although sterile chyle is not thought to be an irritant, the presence of undrained effusions can cause pleural thickening and corresponding atelectasis of the lung.

Changes: None

10. Line 83. What was the anatomical level of TD embolization?

    Response: The thoracic duct was embolized around T3-4, which has been added to the manuscript.

    Changes: Added T3-4, line 88

11. Line 87. Figure 2. Can the leakage point be pointed out by an arrow?

    Response: Thank you for your commentary – we have attempted to outline any areas of leakage, though we believe there were multiple porous channels less than 1 mm in size, which in part, is what makes this problem such a challenge to manage.

    Changes: Added sentence regarding porosity, lines 182-183

12. Line 90. A more detailed description is required to explain the relationship between thoracic duct embolization and bile duct leakage. Was the TD embolized below the diaphragmatic level? Was there a complication during the procedure of TD catheterization?

    Response: Thank you, we will add more detail. The access point is through the cisterna chyli, so bile duct/liver injuries are known complications. There were no complications during the procedure.

    Changes: Added context, lines 95-97 and 158-160

13. Line 95. Any pleural fluid culture (from IPC) performed?

    Response: Yes, bacterial cultures grew S. epidermidis.

    Changes: Added microbial analysis, lines 104-105

14. Line 96. What kind of intrapleural lytic therapy was used?

    Response: Thank you – per MIST protocol, combination Dornase alteplase were instilled. This has been added to the manuscript.

    Changes: Added lytics, lines 103-104

15. Line 102 and 107. It was mentioned that no extravasation was identified during CT lymphangiogram, but it was later noted weeping from the thoracic duct. Please clarify. Was the rate of weeping too slow to be identified on the CT?

Response: Thank you for your question, our proposed hypothesis is that the rate would likely have been too slow to be clearly identified on CT.

Changes: None

16. Line 107. Where was the leaking point of the thoracic duct?

Response: Unfortunately, there was not a single identifiable point of leakage, but numerous locations within 1mm in size which appeared to have weeping, suggestive of chyle leakage.

Changes: None

17. Line 116 and 177. Were those chest tubes not initially put on under-water seal drainage?

Response: Thank you for your question. Line 126-127 indicates all chest tubes were placed to water seal before any removal.

Changes: None

18. Line 120. Was medium-chain triglyceride supplement given in addition to low-fat diet?

Response: The authors did not supplement, as the patients nutritional labs showed a sufficient pre-albumin, she was not losing any weight, and she was tolerating low-fat diet without any complications.

Changes: None

19. Lines 119 and 122. Was doxycycline sclerotherapy applied twice? Please describe the route of administration.

Response: Yes, doxycycline sclerotherapy was injected twice through the breast drain. After instillation, the drain is capped for 30 minutes, and then aspirated out. This has been added to the manuscript.

Changes: Added context, line 128-129

20. Lines 167 to 161. These descriptions should be moved to the end of the Case Description.

Response: We agree with the reviewers thoughtful review and have made the suggested change.

Changes: See lines 137-141

21. Line 173. I am doubtful about the disease labelling “iatrogenic chylothorax”, as there was no direct evidence showing the linkage between chest tube insertion for pneumothorax causing an immediate occurrence of chylous effusion.

Response: Thank you for the reviewers’ comment. However, given the timeline of symptomatology and events, the occurrence between the chylous effusion and chest tube insertion appear to be directly related. Though the patient may have had aberrant congenital lymphatics (which is most likely the case), the authors believe it was the disruption of these lymphatics with an intervention that resulted in the following outcome.

Changes: None

Minor comments:

1. For the first appearance of abbreviations, consider displaying their full names first followed by abbreviations in brackets.

   Response: Thank you, we will incorporate the suggested changes.

   Changes: Added all abbreviations, see lines 18, 28, 29, 74-75, 83, 95, 98, 131, 132
2. “Chylothorax management remains understudied with few high-quality trials guiding treatment.” (First sentences of conclusions in the abstract). Although this is a generally accepted statement, this is not reflected in the case report. Consider removing this sentence.

   Response: Thank you, what the authors mean by this statement is that though there are multiple options in how to treat chylothorax, due to the rarity and unpredictability of the problem, there is no great standardized algorithms in how to manage as compared to a traumatic chylothorax following esophagectomy for example. We will incorporate suggestions and rephrase accordingly.

   Changes: Rephrased, line 33-34
3. Lines 53 and 54. “Thoracic duct/leak ligation”. Please separate the terms properly, instead of using “/”.

   Response: Thank you for the comment.

   Changes: Added “and/or” for clarity, line 56
4. Line 166. Consider changing “, increasing porosity” to “duct and increased porosity”

   Response: Thank you for the comment.

Changes: Added “thereby” for clarity, line 187

Reviewer B

How did the chylothorax fistulize to the breast - was any investigation done to ensure this wasn't a malignancy of the breast?

Response: We are unable to determine precisely how the fistula developed. We suspect this likely resulted from long-standing, undertreated chylothorax. She had undergone screening mammography 5 months prior to presenting to our facilities. Upon presentation, she underwent CTs that did not reveal anything suspicious for malignancy. Diagnostic thoracentesis did not reveal anything suggestive of malignancy.

Changes: None

what the chyle leak she developed also a complication of the rib biopsy or just spontaneous?

Response: We are unable to determine the exact etiology of the chyle leake as we do not have records from the outside facility and we did not see her until 10 years after this began.

Changes: None

shy did we persist with continuous drainage of the effusion and not intervene.

what complications did she develop due to the pathology?

Response: Unfortunately, this element of her care was conducted at an outside hospital, so we cannot comment on the rationale of the outside providers. Our initial treatment was thoracic duct embolization and IPC placement. While minimally invasive lymphatic interventions generally have a slightly reduced efficacy when compared with surgery, the do not have the reoperative risk. Thus, we sought treatment via less invasive approaches, but she required surgical intervention. Complications the patient experienced due to her pathology was the fistulization and pulmonary emboli. Complications the patient experienced due to her treatment was common bile duct leak and pneumonia.

Changes: None

while on the tpn what was her oral diet?

Response: Clear liquid diet (see line 131)

Changes: None

Did she ever get octreotide?

Response: No

Changes: None

the thought process behind the chosen management?

Response: There remains a dearth of literature surrounding high-output/recurrent chylothoraces. Given the severity of her presentation, it seemed unlikely to resolve with (drainage, TPN, and NPO status). We proceeded with thoracic duct embolization and IPC placement initially. After this was unsuccessful, we proceeded to a hybrid operating room so both thoracic surgery and interventional radiology can work concomitantly. We then performed decortication, pleurodesis, and ligation of the chylous leak. We sought to proceed with less invasive measures initially, but she required invasive interventions to achieve treatment.

Changes: None

Reviewer C

1. please explain all of the abbreviations.

   Response: Thank you, we have incorporated the reviewers' suggestions.

   Changes: Added NPO, ERCP, MRCP, IPC, IR
2. Line 59, what is initial therapy?

   Response: The initial therapy was diuretics, diets, and repeat thoracentesis (see line 69)

   Changes: Added diets, line 69
3. Line 63, nothing is written how the chylothorax was managed initially.

   Response: We do not have access to the patient's outside records. Per patient reporting, she trialed numerous medications, diets and underwent thoracenteses (although not routinely) (see line 69)

Changes: Added diets, line 69

4. Line 79, why did this patient require MRI to diagnose chylothorax?

   Response: We utilized MR lymphangiogram in order to map the patient's lymphatics, identify any areas of leakage/fistulization, and to see lymphatic flow.

   Changes: None

5. You should not write legend of figures in the middle of the text.

   Response: thank you, we have adjusting the legend accordingly.

   Changes: Changed figure descriptions to below the figures on pages 9-10

6. Line 119, why did you start diet after removing chest tubes? Usually, it is opposite.

   Response: A clear liquid diet was initiated when the patient had three chest tubes in place (see line 123). Only one was removed at the time she began eating (see line 129-130).

   Changes: None

Reviewer D

Very rare and interesting case and very well managed case.
If authors could provide pleural fluid analysis of the diagnostic thoracentesis when done at authors center would give more information. Also say if it is exudative or transudative chylothorax.

Very well written

Response: Thank you for your comments.
Changes: Adjusted to add exudative and triglyceride number lines 82-84