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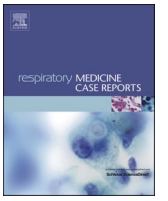

Case Report

Double trouble: Biochemically confirmed bilateral chylothorax with positive pleural fluid cytology due to breast adenocarcinoma

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ABSTRACT

Although chylothorax is a well-described complication of malignancy, especially lymphoma, breast adenocarcinoma has not been a commonly implicated primary tumor. There has been only one published report of biochemically confirmed bilateral chylothorax in solid malignancy, and this was not associated with breast adenocarcinoma. Likewise, there has been only one published report of bilateral chylothorax in solid malignancy with positive pleural fluid cytology on both sides; again, the primary tumor was not breast adenocarcinoma. Herein we present a case that combines all three of these rarely reported features: a patient with metastatic breast adenocarcinoma who developed biochemically confirmed bilateral chylothorax with documented positive pleural fluid cytology on both sides. This report is accompanied by a literature review of published cases of bilateral chylothorax in solid malignancy.

1. Introduction

Chylothorax is defined as the abnormal accumulation of chyle-containing lymphatic fluid within the pleural space. Malignancy and trauma—whether iatrogenic or non-iatrogenic—are the most common culprits. In the category of malignancy, lymphoma predominates while solid tumors have been implicated less frequently. We present the case of a woman with metastatic breast cancer who not only developed biochemically confirmed bilateral chylothorax, itself a rarely described complication of carcinoma, but was also found to have malignant cells in both pleural effusions. Our case is accompanied by a search of the literature for other reports of biochemically confirmed bilateral chylothorax with pleural fluid cytology positive for carcinoma on both sides. We were unable to find another complete description of this exact combination in any patient with solid malignancy.

2. Case presentation

A 59-year-old female presented to our institution for gradually worsening dyspnea. Her past medical history was significant for left breast adenocarcinoma initially diagnosed 11 years earlier and managed with bilateral mastectomy plus adjuvant chemoradiotherapy. Two years prior to presentation, recurrence with metastases to the lung was diagnosed. She was started on a regimen of Paclitaxel and Atezolizumab, which was eventually switched to Gemcitabine due to concern for pulmonary toxicity. Over the past year, chemotherapy had changed from Gemcitabine to Sacituzumab Govitecan, then to Capecitabine, and finally to Doxorubicin due to disease

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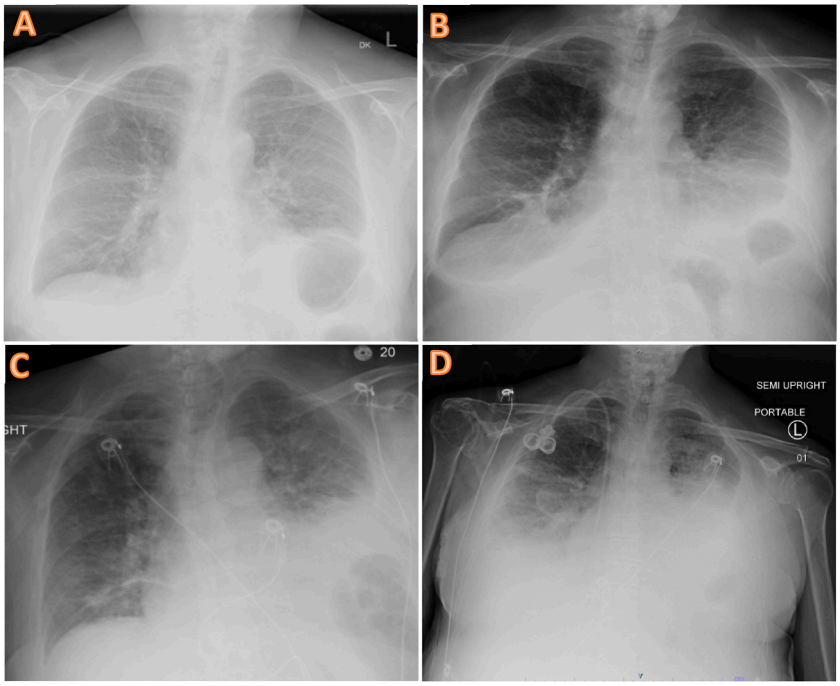

Fig. 1. (A) Frontal chest radiograph (CXR) taken 1 month prior to hospital admission showing elevated left hemidiaphragm with no evidence of pleural effusion. Elevated left hemidiaphragm had been present on prior imaging studies. (B) Initial CXR from first hospital admission showing bilateral pleural effusions confirmed by subsequent computed tomography. (C) CXR obtained after right thoracentesis showing improvement of right pleural effusion with similar left pleural effusion. (D) CXR from second hospital admission showing recurrence of right pleural effusion and worsening left pleural effusion.

progression.

On admission, she was visibly dyspneic. Physical examination was significant for decreased breath sounds in the lower lung fields. Routine laboratory evaluation was unremarkable. While no pleural effusions had been present on a chest radiograph (CXR) from one month prior (Fig. 1A), current admission CXR demonstrated new bilateral pleural effusions (Fig. 1B) confirmed by subsequent computed tomography (CT) of the chest (not shown). Worsening signs of lymphangitic and hepatic metastases were also noted on the CT as were minimally enlarged prevascular mediastinal lymph nodes. The patient underwent right thoracentesis with drainage of 850ml of dark yellow pleural fluid (PF). Fluid analysis showed a WBC count of 1600/mm3 (77% lymphocytes), lactate dehydrogenase (LDH) of 402 U/L (serum LDH 1000 U/L), total protein of 4.3g/dl (serum total protein 7.3g/dl), cholesterol of 84mg/dl, and triglycerides of 129mg/dl. Cytology was positive for malignant cells consistent with metastatic breast adenocarcinoma.

The patient's CXR improved after thoracentesis (Fig. 1C), as did her symptoms. She was discharged but was then readmitted one week later for recurrence of dyspnea. On repeat CXR, reaccumulation of moderate right pleural effusion was noted with interval progression of a large left pleural effusion (Fig. 1D). Left thoracentesis yielded 650ml of clear yellow PF. Fluid studies showed WBC count of 611/mm^3 (lymphocytes 29%), LDH of 499 U/L (serum LDH 1157 U/L), total protein of 3.4 g/dl (serum total protein 6.3 g/dl), cholesterol of 71 mg/dl, and triglycerides of 177 mg/dl. Cytology was once again positive for malignant cells consistent with metastatic breast adenocarcinoma.

Her dyspnea decreased modestly after drainage of bilateral pleural effusions. The patient was deemed unfit for further disease-modifying therapy and was discharged home with hospice services.

3. Discussion

Chylothorax results from the accumulation in the pleural space of chyle-containing lymphatic fluid normally flowing through the thoracic duct (TD) and accounts for 2%–4% of pleural effusions [1,2]. The appearance of PF is commonly described as turbid or milky, but that is a variable finding. Diagnosis is typically established by PF analysis demonstrating triglyceride levels greater than 110 mg/dL and cholesterol levels less than 200 mg/dL. The gold standard for diagnosis is the identification of chylomicrons by lipoprotein electrophoresis [3]. Pseudochylothorax should be considered for fluid cholesterol levels above 200mg/dl and fluid to serum cholesterol ratio of more than 1 [4].

Chylothorax occurs when the integrity or patency of the TD is interrupted. Surgery and trauma account for approximately half of cases while malignancy underlies about 17% [5]. When chylothorax is caused by malignancy, lymphoma accounts for up to two thirds of cases. Doerr et al. [5] identified 23 out of 34 (68%) patients with malignancy complicated by chylothorax to have lymphoma, 5 (15%) patients to have chronic lymphocytic leukemia, 5 (15%) to have unspecified metastatic disease, and 1 (3%) to have lung cancer. Teng et al. [6] reported similar results, with lymphoma accounting for 11 out of 18 cases (61%). Of the 7 (39%) solid tumors, 3 (17%)

Table 1
Summary of previously published reports of bilateral chylothorax in the setting of solid malignancy.

Author	Diagnosis	Pleural Fluid specimen tested	Pleural Fluid Cytology	Appearance	Chylomicrons	Triglycerides (mg/dl)	Cholesterol (mg/dl)
Abounasr et al. [8]	Nasopharyngeal carcinoma[a]	Right	NR	Milky white	NR	125	NR
Altinoz et al. [9]	Low differentiated adenocarcinoma with signet cells	Only 1 set of results unclear from which side	Lymphocytes with atypical mesothelial cells	Cloudy, milky	NR	165	85
Gutierrez Macias et al. [7]	Metastatic adenocarcinoma of unknown primary	Bilateral	Negative	Milky (both)	Positive on both sides	Right: 433 Left: 163	Right: 143 Left: 126
Kayacan et al. [10]	Signet-ring cell adenocarcinoma	Only 1 set of results unclear from which side	Positive	None reported	NR	297	NR
Kurtipek et al. [11]	Malignant mesothelioma	Only 1 set of results unclear from which side	NR	None reported	NR	1228	149
Merza et al. [12]	Pancreaticobiliary vs upper gastrointestinal cancer	Left	Negative	Creamy yellow	NR	1066	53
Mogulkoc et al. [13]	Signet-ring cell carcinoma	Reported to have tested both sides but only 1 set of biochemical analysis results shown	Positive for malignant cells on both sides	Milky	Positive	335	59
Nagano et al. [14]	Gastric cancer	Reported to have tested both sides but only 1 set of biochemical analysis results shown	Negative on both sides	Turbid, yellowish	NR	515	70
Samuel et al. [15]	Gastric adenocarcinoma[a]	Only 1 set of results unclear from which side	Positive	Turbid orange color	NR	123	64
Shibata et al. [16]	Signet-ring cell carcinoma; inflammatory carcinoma	Right	Positive	Milky yellow	Positive	673	132
Wu et al. [17]	Gastric adenocarcinoma	Right	NR	Turbid yellow	Positive	80	53
Zylberman et al. [18]	Infiltrating ductal carcinoma of right breast	Only 1 set of results unclear from which side	Negative	Milky	NR	984	90

NR – not reported.
[a] Published as abstract.

were identified to be lung cancer, 1 (6%) neuroblastoma, 1 (6%) cholangiocarcinoma and 2 (11%) remained unknown. Neither study included any cases of breast cancer.

We performed a literature review to identify detailed reports of chylothorax in solid malignancy. A systematic search was conducted using the terms "bilateral chylothorax" AND "malignancy" in MEDLINE via PubMed® and Google Scholar. This database search identified 258 unique publications, which were screened by title and abstract followed by full-text review of potentially eligible results in the English and Spanish languages. Articles contributing to the literature review had to describe patients with bilateral pleural effusions and report biochemical and cytopathological PF studies. Cases of chylothorax due to lymphoma or as complications of oncological surgery were excluded. A total of 12 articles were ultimately included in the literature review. Of these 12 pertinent publications (Table 1), only one report [7] provided biochemical confirmation of bilateral chylothorax, though the PF was negative for malignant cells on both sides. The other 11 articles [8–18] described occurrence of bilateral chylothorax but confirmatory PF studies were invariably provided from only one side. Among these 11 cases, cytology was positive for 1 case with a primary gastric adenocarcinoma, 1 case with primary low differentiated adenocarcinoma with signet cells and 2 cases with primary signet ring cell carcinoma. One of the 2 reports of signet ring cell carcinoma was authored by Mogulkoc et al., who describe bilateral chylothorax with malignant cells identified on both sides but, as mentioned, provided only one set of biochemical PF results in their report [13]. Included among these 11 reports is a case of right-sided breast cancer with bilateral pleural effusions, at least one of which was sampled and found to be biochemically consistent with chylothorax [18]. The PF specimen was notably negative for malignant cells however. Separately, the aforementioned article by Teng et al. [6] describes a series of 7 cases of chylothorax in solid malignancy but does not specify for any of them whether bilateral pleural effusions were present. Two of the 7 patients had positive PF cytology: one was a case of lung adenocarcinoma and the other of neuroblastoma.

The present case differs from previously published reports in that, firstly, our patient is one with metastatic breast cancer and biochemically proven bilateral chylothorax (Table 2). As mentioned, our literature search identified only one other case of bilateral

Table 2
Characteristics of bilateral pleural fluid analysis from the present case.

Pleural Fluid	Right	Left
Color	Yellow	Yellow
White Blood Cell **(cells/mm^3)**	1600	611
Neutrophils (%)	1	21
Lymphocyte (%)	77	29
Macrophage (%)	10	27
Mesothelial cells (%)	5	20
Monocytes (%)	7	3
Red Blood Cell **(cells/mm^3)**	4000	2000
Lactate dehydrogenase **(U/L)**	402	499
Total Protein **(g/dl)**	4.3	3.4
Triglyceride **(mg/dl)**	129	177
Cholesterol **(mg/dl)**	84	71
Cytology	Positive	Positive

chylothorax in solid malignancy with confirmatory PF analysis from both sides, but that is a case of adenocarcinoma of unknown primary [7]. In the other reports, bilateral chylothorax appears to be assumed based on documented chylothorax on one side and the presence of a contralateral pleural effusion that was not sampled. Somewhat surprisingly, we found only one instance of medical chylothorax in the setting of breast cancer published prior to the present case [18]. On the other hand, our literature review suggests that metastatic gastric malignancy (7 out 12, 58%) could be a potentially common solid tumor causing bilateral chylothorax [9,10, 13–17]. In theory, metastatic breast cancer would be expected to cause chylothorax more often considering its location and propensity to metastasize within the thorax. Left breast lymphatic flow is known to ultimately drain into the TD, which could provide a pathway for spread and eventual TD interruption, potentially causing chylothorax [19]. Secondly, in addition to bilateral confirmed chylothorax, our patient also had malignant cells in both PF specimens. Among the available reports of bilateral chylothorax in solid malignancies (Table 1), only one describes bilateral chylothorax plus bilateral positive PF cytology: the aforementioned report by Mogulkoc et al. [13], but it provides biochemical PF analysis results from only one side. Likewise, most of the other cases did not even demonstrate malignant cells in the documented chylothorax and certainly not on the contralateral side. The sole report of bilateral chylothorax in breast cancer presented negative PF cytology on the sampled side [18].

It is notable that chylothorax due to malignancy is often accompanied by negative PF cytology. Various mechanisms have been postulated for the development of chylothorax in the setting of cancer. Extravasation of chylous lymph into the pleural cavity can result from interruption of the TD wall by direct tumoral invasion, leading to destruction and eventual leakage [20]. Extrinsic compression of the TD by mediastinal lymphadenopathy or by the primary tumor itself is another mechanism. Such compression can impede normal lymphatic drainage into the TD, resulting in back up of TD contents into the pleural space [21]. We speculate that chylothorax with positive malignant cells such as in our patient may result from TD invasion while TD obstruction leads to chylothorax with negative cytology. Another possibility is the coexistence and mixing of chylothorax and malignant effusion in the same pleural space. We propose a terminological distinction between the two scenarios: “malignancy-associated” chylothorax applied to cases with negative cytology while “malignant” chylothorax reserved for cases with positive cytology. It is unknown whether this distinction carries any prognostic significance or whether it should impact management.

4. Conclusion

To our knowledge, this case represents the first complete description not just in breast adenocarcinoma but in any solid malignancy of biochemically confirmed bilateral chylothorax with documented bilateral positive PF cytology. We have also presented the results of an informative literature search for other cases of bilateral chylothorax complicating solid malignancy.

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Authors contributions

RLS: collected patient data, reviewed literature, wrote manuscript, approved final version. AE: searched literature, edited manuscript, approved final version. JM: wrote manuscript, approved final version. TA: edited manuscript, approved final version. OE: conceived project, edited manuscript, approved final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] S. Romero, Nontraumatic chylothorax, Curr. Opin. Pulm. Med. 6 (4) (2000) 287–291, https://doi.org/10.1097/00063198-200007000-00006.
[2] M. Patil, S.S. Dhillon, K. Attwood, M. Saoud, A.H. Alraiyes, K. Harris, Management of benign pleural effusions using indwelling pleural catheters: a systematic review and meta-analysis, Chest 151 (3) (2017) 626–635, https://doi.org/10.1016/j.chest.2016.10.052.
[3] E.E. McGrath, Z. Blades, P.B. Anderson, Chylothorax: aetiology, diagnosis and therapeutic options, Respir. Med. 104 (1) (2010) 1–8, https://doi.org/10.1016/j.rmed.2009.08.010.
[4] V. Skouras, I. Kalomenidis, Chylothorax: diagnostic approach, Curr. Opin. Pulm. Med. 16 (4) (2010) 387–393, https://doi.org/10.1097/MCP.0b013e328338dde2.
[5] C.H. Doerr, M.S. Allen, F.C. Nichols 3rd, J.H. Ryu, Etiology of chylothorax in 203 patients, Mayo Clin. Proc. 80 (7) (2005) 867–870, https://doi.org/10.4065/80.7.867.
[6] C.L. Teng, K.W. Li, J.T. Yu, S.L. Hsu, R.C. Wang, W.L. Hwang, Malignancy-associated chylothorax: a 20-year study of 18 patients from a single institution, Eur. J. Cancer Care 21 (5) (2012) 599–605, https://doi.org/10.1111/j.1365-2354.2012.01329.x.
[7] A. Gutiérrez Macías, E. Lizarralde Palacios, J.M. Merino Múgica, S. Cabeza García, P. Martínez Odriozola, F. Miguel de la Villa, Quilotórax bilateral en un caso de adenocarcinoma metastásico de primario desconocido [Bilateral chylothorax in a case of metastatic adenocarcinoma of unknown primary], An. Med. Interna 23 (4) (2006) 176–178, https://doi.org/10.4321/s0212-71992006000400007.
[8] K.K. Abounasr, D. Poch, D. Addrizzo-Harris, A case of metastatic nasopharyngeal carcinoma causing bilateral chylothoraces, Chest 134 (4) (2008) 61C, https://doi.org/10.1378/chest.134.4_MeetingAbstracts.c61002 (abstract).
[9] H. Altinöz, R. Baran, F. Kargin, B. Keser, V. Baysungur, Chylothorax-literature review and two rare cases, Turk. Thorac. J. 9 (1) (2008) 56–60.
[10] O. Kayacan, D. Karnak, B. Ayşe Can, S. Dizbay Sak, S. Beder, Gastric signet-ring cell adenocarcinoma presenting with left arm deep-vein thrombosis and bilateral chylothorax, Clin. Appl. Thromb. Hemost. 14 (4) (2008) 476–480, https://doi.org/10.1177/1076029607309181.
[11] E. Kurtipek, M.İ. Eren Karanis, N. Düzgün, H. Esme, M. Çaycı, A cause of bilateral chylothorax: a case of mesothelioma without pleural involvement during initial diagnosis, Case Rep. Pulmonol. 2015 (2015), 962504, https://doi.org/10.1155/2015/962504.
[12] N. Merza, J. Lung, M. Saadaldin, T. Naguib, Bilateral chylothorax as a unique presentation of pancreaticobiliary or upper gastrointestinal cancer, Case Rep. Pulmonol. 2019 (2019), 9387021, https://doi.org/10.1155/2019/9387021.
[13] N. Mogulkoc, B. Onal, N. Okyay, O. Günel, U. Bayindir, Chylothorax, chylopericardium and lymphoedema–the presenting features of signet-ring cell carcinoma, Eur. Respir. J. 13 (6) (1999) 1489–1491.
[14] N. Nagano, M. Suzuki, K. Tamura, S. Kobayashi, Y. Kojima, G. Naka, et al., Refractory chylothorax and lymphedema caused by advanced gastric cancer, Intern. Med. 58 (21) (2019) 3143–3148, https://doi.org/10.2169/internalmedicine.2351-18.
[15] A. Samuel, J. Mathew, A. Sharaan, A rare case of chylothorax shrouding a malignant pleural effusion, Chest 156 (4) (2019) A1224, https://doi.org/10.1016/j.chest.2019.08.1107 (abstract).
[16] K. Shibata, S. Kitagawa, M. Fujimura, T. Matsuda, Chylothorax associated with inflammatory carcinoma, Intern. Med. 37 (6) (1998) 538–541, https://doi.org/10.2169/internalmedicine.37.538.
[17] J. Wu, L. Lv, K. Zhou, J. Huo, Chylothorax and lymphedema as the initial manifestations of gastric carcinoma: a case report and review of the literature, Oncol. Lett. 11 (4) (2016) 2835–2838, https://doi.org/10.3892/ol.2016.4285.
[18] M. Zylberman, F. Losco, C. Nicolini, S. Halac, K. Patane, F. Petracci, Quilopericardio y quilotórax bilateral en una mujer con cáncer de mama [Chylopericardium and bilateral chylothorax in a breast cancer patient], Medicina (B Aires) 74 (1) (2014) 62–63.
[19] S. Standring, The anatomy of the vascular and lymphatic systems, in: Gray's Anatomy, 42nd edition, Elsevier, 2021, p. 1464.e56, 1464.e129.
[20] C. Cholet, C. Delalandre, L. Monnier-Cholley, F. Le Pimpec-Barthes, S. El Mouhadi, L. Arrivé, Nontraumatic chylothorax: nonenhanced MR lymphography, Radiographics 40 (6) (2020) 1554–1573, https://doi.org/10.1148/rg.2020200044.
[21] J.T. Huggins, Chylothorax and cholesterol pleural effusion, Semin. Respir. Crit. Care Med. 31 (6) (2010) 743–750, https://doi.org/10.1055/s-0030-1269834.

ABBREVIATIONS

CT: computed tomography
CXR: chest radiograph
LDH: lactate dehydrogenase
PF: pleural fluid
TD: thoracic duct
WBC: white blood cell