Respiratory Medicine Case Reports 20 (2017) 188–191

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Transudative pleural effusion of malignant etiology: Rare but real

Lindsey Johnson, MD [a], Hafiz Abdul Moiz Fakih, MD [b], Salim Daouk, MD [b], Shaheera Saleem [a], Ali Ataya, MD [b, *]

[a] University of Florida, Department of Internal Medicine, Gainesville, FL, USA
[b] University of Florida, Division of Pulmonary, Critical Care, and Sleep Medicine, Gainesville, FL, USA

ARTICLE INFO

Article history:
Received 5 February 2017
Received in revised form
23 February 2017
Accepted 27 February 2017

Keywords:
Light's criteria
Pleural effusion
Transudate
Cytology
Immunohistochemistry

ABSTRACT

A 62-year-old female presented to the emergency room with one-month history of epigastric abdominal pain, nausea and vomiting. She endorsed progressive dyspnea over two weeks. CT of the abdomen demonstrated bilateral pleural effusions and pancreatic inflammation, so the working diagnosis was pancreatitis. A diagnostic thoracentesis was performed and the pleural fluid analysis was classified as transudate by Light's criteria. Given the atypical features in history and concern for malignancy, fluid was sent for cytological examination and immunohistochemistry which suggested a mucinous malignancy. EGD revealed poorly differentiated signet ring cell adenocarcinoma of stomach. Patient underwent placement of indwelling pleural catheters for symptomatic improvement and was discharged to hospice. The decision whether to routinely send transudative effusions for cytological evaluation remains controversial. This case demonstrates the importance of using clinical judgement to guide that decision.

1. Introduction

In this era of cost effective medicine, it is essential to ensure that we do not sacrifice quality of care. The traditional teaching is that malignant effusions are rarely transudative and performing cytology to diagnose malignancy on a transudative pleural effusion has a low yield and might not be cost effective. Our case demonstrates the importance of integrating clinical judgement into making this decision. In this case, when malignancy was suspected as a possible etiology, we sent the transudative effusion for cytological analysis. We were able to use these results to diagnose our patient with metastatic gastric adenocarcinoma. Reports of cases in which malignant pleural effusion (MPE) was the initial presentation of gastric adenocarcinoma note the mean survival time at diagnosis was three months [1]. This further emphasizes the importance of making a diagnosis in a timely manner.

2. Case report

A 62-year-old woman presented to the emergency room (ER) with one-month history of epigastric abdominal pain, nausea and nonbloody nonbilious emesis accompanied by a 20-lb weight loss. She also endorsed progressive dyspnea over the past two weeks. She had a history of hypertension, hyperlipidemia, and gastroesophageal reflux disease. There was no history of congestive heart failure, liver cirrhosis, chronic renal failure, or nephrotic syndrome. Her only medications were atorvastatin and a proton pump inhibitor. The patient denied current or previous alcohol use. On examination, her vitals were unremarkable. She was chronically ill appearing and had decreased breath sounds in the lower third of both lungs. Her cardiovascular exam was unremarkable, and she did not have jugular venous distension or any signs of congestive heart failure. Her abdominal exam was notable for midepigastric tenderness but no guarding and she had normal bowel sounds.

At the time of admission her lipase was 205 U/L (Upper limit of normal 60 U/L). Her serum creatinine was 1.56 mg/dL (calculated Creatinine clearance 47.841 ml/min) with a normal baseline. Rest of the labs including the liver enzymes were unremarkable. Chest X-ray (Fig. 1) revealed moderate bilateral pleural effusions. CT abdomen pelvis showed (Fig. 2) diffuse enlargement of the pancreas and pancreatic edema, bilateral pleural effusion, distal thickening of the stomach and decreased perfusion to her left kidney with mild hydronephrosis. She was initially managed as an acute pancreatitis.

The next day she was taken to the operating room where urology placed a left renal stent. No intraluminal obstruction was found. Post-operative course was complicated by hypoxic

* Corresponding author. University of Florida, Division of Pulmonary, Critical Care, and Sleep Medicine, 1600 SW Archer Rd, M452, PO Box 100225, Gainesville, FL, 32610, USA.
E-mail address: aliataya@gmail.com (A. Ataya).

http://dx.doi.org/10.1016/j.rmcr.2017.02.015

Abbreviations

MPE	Malignant pleural effusions
CT	Computed tomography
EGD	Esophagogastroduodenoscopy
mCEA	monoclonal carcinoembryonic antigen

respiratory failure in the recovery area and she was transferred to the medical intensive care unit (MICU). There she had a diagnostic thoracentesis performed, with the thought that removal of the fluid would also help with extubation. She had removal of 1200 ml of straw-colored fluid and was extubated without any complications.

Pleural fluid analysis (Table 1) revealed a transudative effusion by Light's criteria. Despite the transudative nature of the effusion, we decided to send the fluid for cytology as a metastatic malignancy was one of our considerations. Cytology results returned for atypical cells concerning for metastatic carcinoma. Immunohistochemistry performed on the cell block prepared from the fluid was positive for Ber-EP4 and monoclonal carcinoembryonic antigen (mCEA). EGD was performed (Fig. 3) showing infiltrative process in the stomach. Surgical pathology revealed poorly differentiated adenocarcinoma with signet ring features.

The patient and the family decided to take the route of hospice care. She had symptomatic, recurrent pleural effusion for which she had placement of bilateral indwelling pleural catheters.

3. Discussion

When evaluating a new pleural effusion, it is standard practice to determine if it is an exudate or transudate based on Light's Criteria. Cytological study of the fluid can then be requested to determine the presence of malignancy. If the fluid has been classified as a transudate, many studies have shown that further cytological investigation would be low yield since most MPE are exudates [2–4]. Instead of sending for further testing, it is recommended to investigate for the etiology of the transudate, including congestive heart failure, cirrhosis and renal failure [2]. Some literature suggests that every effusion should be sent for cytology to maximize the yield of an invasive test [4–6]. The British Thoracic Society (BTS) recommends a thoracentesis should not be performed for bilateral pleural effusions which are clinically suspected of being a transudate unless there are atypical features or the effusions fail to respond to therapy [7]. If fluid is sampled, the BTS recommends sending all fluid for cytology.

Our knowledge regarding diagnostic utility of pleural fluid cytology has greatly expanded over the years. A 2014 study which analyzed 840 MPE found that cytology was 59% accurate in identifying malignancy [8]. To further maximize diagnostic yield, it is recommended to use both cell blocks and smears from pleural fluid samples [7]. After sending fluid twice for cytology, the diagnostic yield greatly decreases with sending a third sample for cytology and it is recommended to obtain a pleural needle biopsy [9].

Mechanisms of exudative MPE include lymphatic obstruction and pleural seeding of the malignancy [10]. Possible pathophysiological explanations of a transudative MPE include: (i) the initial accumulation of fluid may be primarily caused by lymphatic obstruction rather than pleural seeding, thus the pleural fluid would be an ultrafiltrate with low protein levels (ii) confounding co-morbidities such as heart failure responsible for the fluid accumulation rather than tumor (iii) concomitant atelectasis from bronchial obstruction [11]. The most common tumors associated with pleural effusions are lung, breast and lymphoma; these types of tumors also frequently invade mediastinal lymph nodes [12]. In a case series by Ashchi et al. [4], it was concluded that most transudative MPE result from a coexistent transudative state and when a clinician has any suspicion of malignancy they should proceed with cytology.

In a retrospective study by Ryu et al. [3] only 7 (3.1%) of 229 patients with MPE had transudates. This value fits within the range of 1–10.6% found in other studies. Foresti et al. [10] reported a retrospective study in which four of 106 (3.8%) patients with positive cytological exam for malignancy were transudative by Light's criteria. Because the median survival after diagnosis of a MPE is only 4–9 months, it is essential to utilize cytology in any patient suspected of having a malignancy [13].

Ferreiro et al. [14] have proposed two models to predict when a transudative effusion may be malignant. Model 1 used clinic-radiological variables (location of pleural effusion, chest imaging findings consistent with malignancy, presence of dyspnea, and serosanguinous appearance of pleural fluid) and Model 2 (the variables of Model 1 plus carcinoembryonic level [CEA]). In their study, 26 (9.3%) of 281 transudates were found to be malignant.

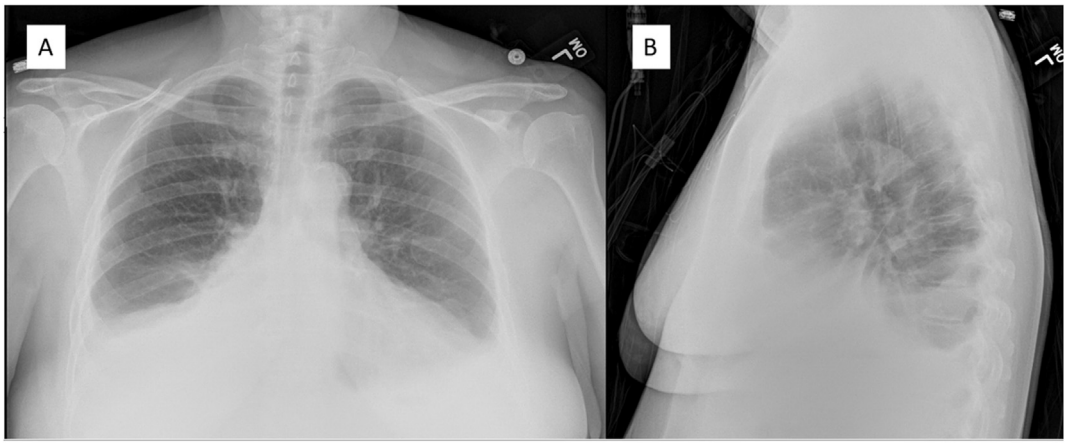

Fig. 1. Chest X-ray posteroanterior (A) and lateral (B) views showing bilateral pleural effusions, with bibasilar opacification, most likely from compressive atelectasis.

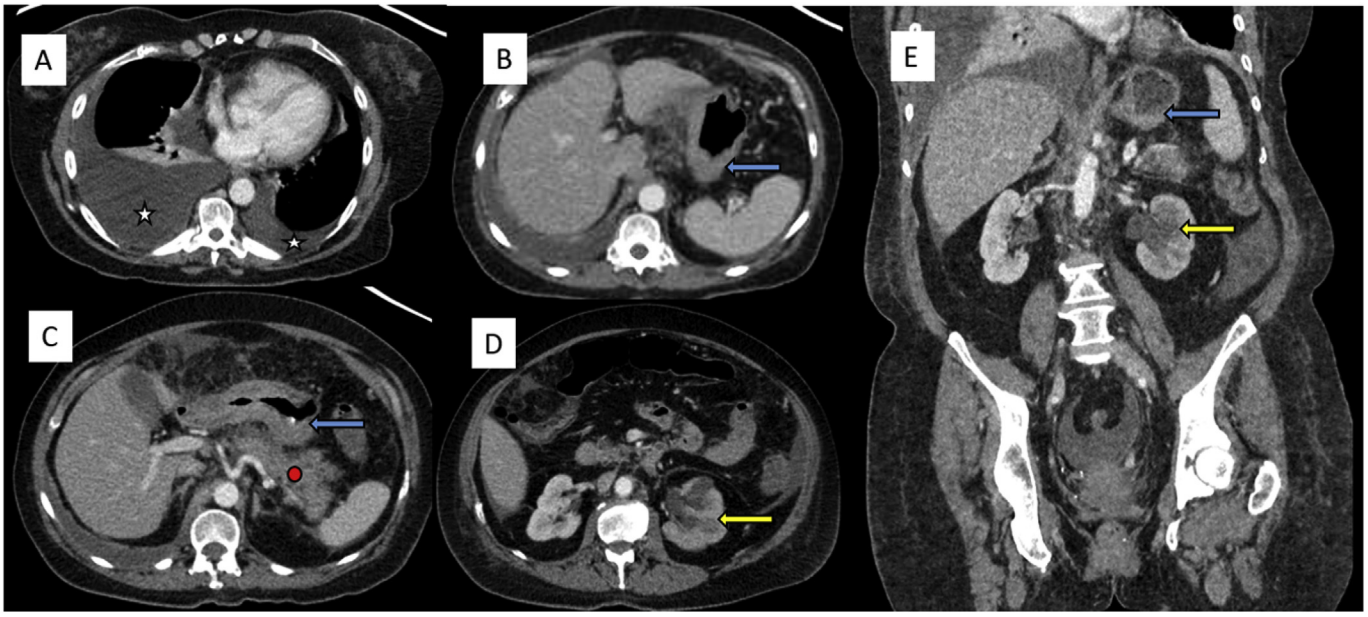

Fig. 2. Computed tomography (CT) of the abdomen and pelvis with intravenous contrast representative axial (A–D) and coronal (E) sections showing bilateral pleural effusion (white star) right greater than left with underlying compressive atelectasis, thickening of the distal part of the stomach (blue arrows) and an enlarged, edematous uniformly enhancing pancreas (red dot). There was differential perfusion and excretion of the kidneys with the left kidney (yellow arrow) hypoenhancing relative to the right, mild left hydronephrosis without any identified obstructing lesion. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Results of diagnostic thoracentesis.

LDH Serum	196 U/L
LDH fluid	<10 U/L
Total protein serum	5.9 g/dL
Total protein fluid	<0.2 g/dL
Albumin serum	2.7 g/dL
Albumin fluid	<0.2 g/dL
Glucose fluid	<2 mg/dL
Cell count fluid	350 WBC/mm^3
pH	7.51
Gram stain	Negative
Culture	Negative
Creatinine fluid	<0.06 mg/dL
Amylase fluid	<3 U/L

Using logistic regression analysis, they calculated Area under the curve (AUC) as follows: Model 1 = 0.973 and Model 2 = 0.995. When we applied Model 1 to our case, the calculated predicted probability of malignant origin of the pleural effusion was 1%. The authors had recommended that cytology should be indicated in patient with a probability of a MPE of 3%. No calculation could be performed using Model 2 as we did not measure the pleural fluid CEA level. This study presents the largest cohort of such patients reported to date, but is still limited by the small number and recruitment only at a single center. As mentioned by the authors, multicenter studies with higher number of patients are required to develop and validate predictive models for transudative MPE.

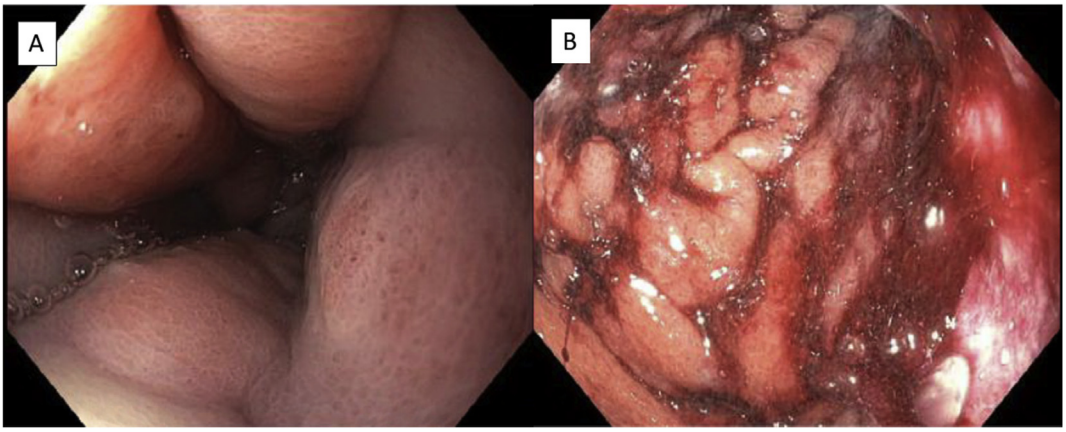

Fig. 3. Upper GI Endoscopy with representative endoscopic images of the gastric body (A) with mucosal changes consistent with infiltrative disease. Images of the greater curvature of the stomach (B) showed marked enlargement of the folds in mid-body of stomach extending to proximal antrum. The folds along the lesser curvature were absent and replaced with a hard, plaque-like infiltration. The mid body of the stomach was severely narrowed by this process, causing partial obstruction.

4. Conclusion

Not all transudative pleural effusions are benign and the clinician should rely on the entire clinical picture when deciding whether to order pleural fluid cytology. We ran our case through a new predictive model for transudative malignant effusion, and found that the calculated probability was low, although our case was a cytologically proven transudative MPE. Continued research in this field is required until we reach a well-validated clinico-radiological predictive tool. Until then, due to the poor prognosis of MPE, the clinician should not hesitate to order pleural fluid cytology when clinically suspected. Diagnostic yield of pleural fluid samples increases when both cell blocks and smears are used.

Conflicts of interest

None.

References

[1] A. Roussos, D. Patsopoulos, N. Philippou, Pleural effusion as the initial manifestation of gastric adenocarcinoma: a report of four cases, Scand. J. Gastroenterol. 36 (7) (2001) 784.
[2] Z. Assi, J.L. Caruso, J. Herndon, E.F. Patz, Cytologically proved malignant pleural effusions: distribution of transudates and exudates, Chest 113 (5) (1998) 1302–1304.
[3] J.S. Ryu, S.T. Ryu, Y.S. Kim, J.H. Cho, H.L. Lee, What is the clinical significance of transudative malignant pleural effusion? Korean J. Intern. Med. 18 (4) (2003) 230–233.
[4] M. Ashchi, J. Golish, P. Eng, P. O'Donovan, Transudative malignant pleural effusions: prevalence and mechanisms, South. Med. J. 91 (1) (1998) 23–26.
[5] Y. Moltyaner, M.S. Miletin, R.F. Grossman, Transudative pleural effusions: false reassurance against malignancy, Chest J. 118 (3) (2000) 885.
[6] D.J. Castro, G.D. Nuevo, E. Perez-Rodriguez, Cytologically proved malignant pleural effusions, Chest J. 114 (6) (1998) 1798.
[7] C. Hooper, Y.C.G. Lee, N. Maskell, Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010, Thorax 65 (Suppl 2) (2010) ii4–ii17.
[8] J.M. Porcel, A. Esquerda, M. Vives, S. Bielsa, Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses, Arch. Bronconeumología (English Edition) 50 (5) (2014) 161–165.
[9] V.V. Garrido, E.C. Viedma, A.F. Villar, A. de Pablo Gafas, E.P. Rodríguez, J.M.P. Pérez, et al., Normativa sobre el diagnóstico y tratamiento del derrame pleural. Actualización, Arch. Bronconeumología 50 (6) (2014) 235–249.
[10] V. Foresti, N. Scolari, A. Villa, Positivity of pleural fluid cytologic examination in transudative pleural effusions, Chest J. 114 (6) (1998) 1798–1799.
[11] S.A. Sahn, Malignancy metastatic to the pleura, Clin. Chest Med. 19 (2) (1998) 351–361.
[12] T.J. Bedient, A.I. Musani, Malignant pleural effusions, Pak. J. Chest Med. 18 (1) (2015).
[13] H.-S. Nam, Malignant pleural effusion: medical approaches for diagnosis and management, Tuberc. Respir. Dis. 76 (5) (2014) 211–217.
[14] L. Ferreiro, F. Gude, M.E. Toubes, A. Lama, J. Suárez-Antelo, E. San-José, et al., Predictive models of malignant transudative pleural effusions, J. Thorac. Dis. 9 (1) (2017) 106–116.