March 2013 Pulmonary Case of the Month: Don’t Rein Me In

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History of Present Illness
A 70 year old man was referred for a pleural effusion. The patient had pitting edema of the lower extremities noted in March, 2013. At that time a myocardial perfusion study and an echocardiogram were interpreted as being normal with an ejection fraction of 55%. His primary care physician stopped the amlodipine he was taking for hypertension and his edema resolved. However, the amlodipine was restarted a few weeks later for blood pressure control.

PMH, SH, FH
He has a past medical history of hypertension and asthma. He was diagnosed with prostate cancer in mid 2012. At that time a CT scan of his abdomen/pelvis and a MRI of his pelvis were negative for metastatic disease. He underwent robot assisted radical prostatectomy and bilateral pelvic lymph node dissection in August 2012. His final diagnosis was Gleason 4+5 disease present throughout the prostate with focal extraprostatic extension and lymphovascular and perineural invasion and invasion of right seminal vesicle. He was staged T 3B. Present medications
- Amlodipine 5 mg at bedtime
- Omelsartan (Benicar®) 40 mg/day
- Salmeterol/fluticasone (Advair®) 100/50 1 puff twice a day
- Clonazepam 0.5 mg twice a day
- Lycopene 10 mg daily
He has a 10 year smoking history but no alcohol or drug use. Family history is unremarkable.

Physical Examination
Vital signs: Normal
Lungs: Decreased breath sounds in both lung bases
Heart: Elevated JVP; Normal S1 and S2
Abdomen: Negative
Extremities: 2-3+ pitting edema

Laboratory
- CBC: normal
- Electrolytes: normal
- Serum creatinine: 1.0 mg/dL
- Total protein: 6.8 g/dL
- Albumin: 4.3 g/dL
- NT-pro brain naturetic peptide (BNP): 255 pg/ml

**Radiography**

Chest x-ray is shown in figure 1.

![Figure 1. PA (panel A) and lateral (panel B) chest radiography.](image)

Which of the following is **false**?

1. The patient’s chest x-ray shows bilateral pleural effusions right larger than left
2. A NT-pro BNP 255 pg/ml makes heart failure an unlikely diagnosis
3. His pleural effusion is most likely due to metastatic prostate cancer
4. A normal heart size on chest x-ray excludes heart failure
5. A normal echocardiogram excludes heart failure
Correct!

3. His pleural effusion is most likely due to metastatic prostate cancer

His chest x-ray shows bilateral pleural effusions right greater than left. A NT-pro BNP of <300 pg/ml has a 98% negative predictive value in excluding acute heart failure (1). Prostate cancer most commonly metastasizes to regional lymph nodes and bone (2). Pleural metastases are rare. Nearly half of patients with symptoms of heart failure are found to have a normal left ventricular (LV) ejection fraction (3). Similarly, radiographic variables on chest x-ray have high specificity (79-99%) but modest sensitivity (1-54%) for the diagnosis of heart failure (4). Chest CT could provide clues to the diagnosis such as suggesting an endobronchial obstruction, pleural metastasis, etc. and was therefore performed (Figure 2).

![Representative image from thoracic CT scan.](image)

Which of the following is **false**?

1. The patient’s CT scan shows bilateral pleural effusions right larger than left
2. The whitish area in the region of the liver most likely represents a metastasis
3. The most common cause of bilateral pleural effusions is heart failure
4. Thoracentesis will be necessary to separate a transudate from an exudate in this patient
5. Transudates are most commonly due to congestive heart failure
Correct!

2. The whitish area in the region of the liver most likely represents a metastasis

The CT shows bilateral pleural effusions right larger than left. By convention CT scans are shown as if viewing from the feet towards the head, i.e., the right side of the patient is displayed on the left. The patient’s image is from a contrast-enhanced CT scan and the whitish area is a blood vessel.

Management of pleural effusions usually begins with thoracentesis to separate transudates from exudates (4).

A thoracentesis was performed and yielded pale yellow clear fluid with the following values:
- Negative cytology
- Pleural fluid protein 3.4 gm/dL
- Pleural fluid LDH 87 IU/L

Which of the following is false?
1. The values are most consistent with a transudate
2. 15-20% of pleural effusions due to heart failure are exudates
3. Diuretics increase the proportion of exudative effusions in heart failure
4. Elevated adenosine deaminase in the pleural fluid is diagnostic of heart failure
5. Pleural fluid glucose is usually normal in heart failure
Correct!
4. Elevated adenosine deaminase in the pleural fluid is diagnostic of heart failure

Transudates are characterized by low pleural fluid protein (<0.5 compared to serum) and a low LDH (pleural fluid LDH/serum LDH level ≤ 0.6, or pleural fluid LDH level ≤ 2/3 the upper normal limit for serum LDH) (4). These are known as the Light criteria. The patient’s serum LDH was 210 IU/L and so the effusion is consistent with a transudate. The primary problem with the Light criteria is that they identify 15% to 20% of effusions secondary to heart failure as exudative effusions. This situation is particularly likely if the patient has been receiving diuretics before the thoracentesis. If tuberculous pleuritis is suspected, a pleural fluid ADA level should be obtained. Pleural fluid ADA levels more than 40 U/L in a patient with predominantly lymphocytes in their pleural fluid are virtually diagnostic of tuberculous pleuritis (4). ADA levels are normal in heart failure. Pleural fluid glucose is usually normal in heart failure (4).

The most common cause of bilateral transudative effusions is heart failure (4). However, the patient’s normal heart size, normal systolic function on echocardiogram and the low NT-pro BNP suggest another source.

Which of the following causes of heart failure is best associated with clinical heart failure but a normal heart size, normal systolic function on echocardiogram and a low NT-pro BNP?

1. Ischemic heart disease
2. Mitral regurgitation
3. Aortic regurgitation
4. Alcoholic cardiomyopathy
5. Constrictive pericarditis
Correct!
5. Constrictive pericarditis

All are causes of clinical heart failure. However, most of the other causes are associated with an enlarged heart or enlarged ventricular wall thickness, abnormal systolic function or an elevated NT-pro BNP (5).

Constrictive cardiomyopathy is a disorder where cardiac filling is impeded by a pericardium that is unable to expand sufficiently to adequately fill the ventricular chambers during diastole. The lack of filling results in reduced cardiac output. The percent of the ventricle emptied during systole, the ejection fraction, is normal. An important pathophysiologic feature of constrictive pericarditis is greatly enhanced ventricular interdependence and a dissociation of intracardiac and intrathoracic pressures. Symptoms may be related to fluid overload (edema, anasarca) or to diminished cardiac output (fatigability, dyspnea on exertion). Findings on physical examination include elevated jugular venous pressure (JVP), pulsus paradoxus (an exaggerated drop in systemic blood pressure greater than 10 mmHg during inspiration) and Kussmaul's sign (the lack of an inspiratory decline in JVP).

BNP is released from the atrium in response to the dilatation that occurs in most forms of heart failure. However, with constrictive pericarditis the atrium is not dilated explaining the relatively low NT-pro BNP levels (5).

The restrictive cardiomyopathies have pathophysiology similar to constrictive pericarditis. Both constrictive pericarditis and restrictive cardiomyopathy limit diastolic filling and result in diastolic heart failure, with relatively preserved global systolic function. However, in restrictive cardiomyopathies the etiology is an inability of the heart muscle to adequately stretch while in constrictive pericarditis it is an inability of the pericardium to stretch. Restrictive cardiomyopathies are often secondary to a systemic disorder such as amyloidosis, sarcoidosis, scleroderma, hemochromatosis, eosinophilic heart disease, or as a result of radiation treatment.

Which of the following is true regarding constrictive pericarditis and restrictive cardiomyopathy?

1. Pericardial calcification in a patient with heart failure suggest constrictive pericarditis
2. Cardiac magnetic resonance imaging (CMR) is the best test to separate restrictive cardiomyopathy from constrictive pericarditis
3. Constrictive pericarditis usually responds to medical or surgical therapy
4. Restrictive cardiomyopathy requires medical therapy for the heart failure and may require heart transplantation
5. All of the above
Pericardial calcification strongly suggests constrictive pericarditis when attempting to separate constrictive pericarditis from restrictive cardiomyopathy. Recently, CMR has become an important test in separating the two entities. CMR is advocated by some as the diagnostic procedure of choice for the detection of certain pericardial diseases, including constrictive pericarditis. Our patient’s CMR is shown in Figure 3.

Figure 3. Free breathing cardiac magnetic resonance (CMR) images obtained at the cardiac apex, mid-cavity, and base in the short axis plane show early diastolic interventricular septal flattening and leftward motion during inspiration, representing the so-called "septal bounce."

Characteristic CMR features in patients with constrictive pericarditis include increased pericardial thickening and dilatation of the inferior vena cava, an indirect sign of impaired right ventricular diastolic filling and paradoxical motion of the intraventricular septum. In our patient free breathing CMR images were obtained at the cardiac base, mid-cavity, and apex in the short axis plane. These show early diastolic interventricular septal flattening and leftward motion during inspiration, representing the so-called "septal bounce".

The etiologies of constrictive pericarditis and their relative percentages are shown below (Table 1).

Table 1. Causes and relative percentages of constrictive pericarditis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Idiopathic or viral</td>
<td>42 to 49%</td>
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In each case an initial inflammation of the pericardium is followed by scarring resulting in the constriction.

Which of the following are **appropriate therapies** for constrictive pericarditis?

1. Medical therapy for heart failure
2. Non-steroidal anti-inflammatory drugs (NSAIDS)
3. Corticosteroids
4. Pericardectomy
5. All of the above
Correct!

5. All of the above.

A subset of patients with constrictive pericarditis undergo spontaneous resolution of constrictive pericarditis or respond to medical therapy (17%) (5). A high degree of late gadolinium enhancement (LGE) of the pericardium on CMR appears promising as a way to predict which patients with constrictive pericarditis will have reversal or resolution of the process and not require pericardectomy.

Our patient was medically managed with diuresis which resulted in a 20 lb weight loss and improvement in his symptoms, cardiac examination and chest x-ray (Figure 4).

![Figure 4. PA (Panel A) and lateral (Panel B) chest x-ray after diuresis.](image)

Because his gadolinium uptake was high in his pericardium, he is beginning a 3 week course of prednisone.

**References**


