Brain natriuretic peptide and shortness of breath in the emergency department

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A 54-year-old woman presented to the emergency department with increasing shortness of breath over four days. She reported an increased cough over the previous two months and that her daughter recently had an upper respiratory tract infection. The patient had metastatic breast cancer (estrogen-receptor positive, human epidermal growth factor receptor 2/neu negative). She had received first-line paclitaxel chemotherapy four years earlier, but severe neuropathy developed; her regimen was changed to doxorubicin weekly, with good response and a maximum lifetime cumulative dose of 450 mg/m^2. Restaging performed three months before this visit showed progression in the liver, resulting in a new regimen that included everolimus and exemestane. The patient also had a brief history of treated hypertension a few years earlier but did not take any other medications. Review of systems was negative for fever, pleuritic chest pain and asymmetric calf tenderness.

In the emergency department, the patient's blood pressure was 130/90 mm Hg, heart rate was 86 beats/min, oxygen saturation was 97% on room air and oral temperature was 36.6°C. Her jugular venous pressure was difficult to assess. Precordial examination was unremarkable. She had decreased breath sounds at the bases bilaterally on respiratory examination. Abdominal examination was normal. She had no evidence of peripheral edema or clubbing.

Preliminary laboratory findings showed a hemoglobin level of 120 (normal 120–160) g/L, leukocyte count of 5.7 (normal 4.5–11) x10^9/L and platelet count of 234 (normal 130–400) x10^9/L. Her electrolytes were within normal limits, with a sodium level of 142 mmol/L, potassium level of 4.2 mmol/L and bicarbonate level of 26 mmol/L, and the creatinine level was 74 (normal 50–90) µmol/L. Her troponin I level (high sensitivity) was slightly elevated at 55 (normal < 26) ng/L. D-dimer testing was negative. Testing of a nasopharyngeal swab was negative for influenza. Electrocardiography showed sinus rhythm. The patient's chest radiograph is shown in Figure 1.

What are the relevant findings of the chest radiography?

a. The findings are pathognomonic of atypical pneumonia with an infiltrate in the right middle lobe.
b. There is evidence of a Hampton hump suggesting pulmonary infarct and a high suspicion for a pulmonary embolus.
c. There is evidence of chronic obstructive pulmonary disease with flattening of the diaphragms and retrosternal airspace in the lateral view.
d. There are small bilateral pleural effusions, with no obvious cause of shortness of breath.
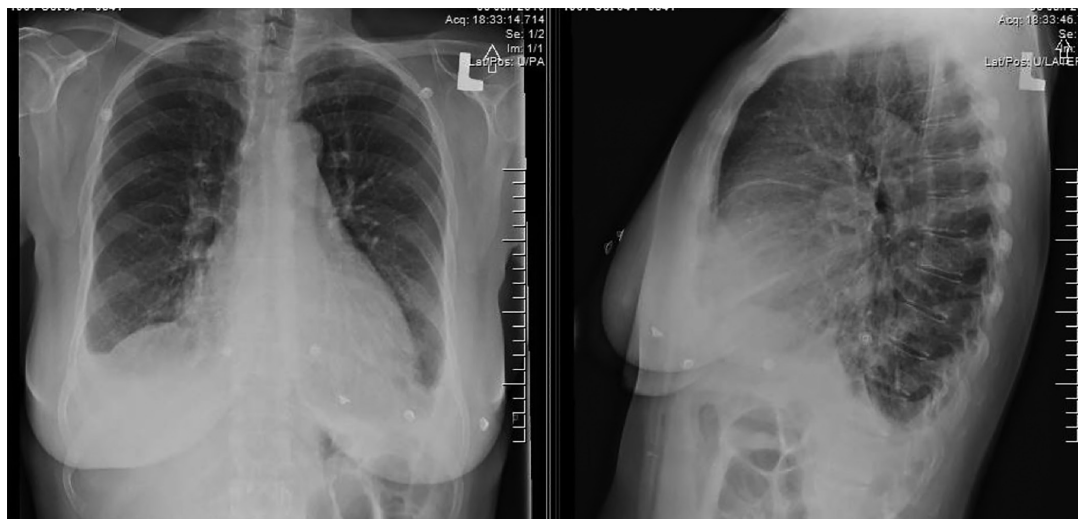

Figure 1: Posteroanterior and lateral views of a chest radiograph in a 54-year-old woman with metastatic breast cancer and increasing shortness of breath.

The correct answer is (d). This chest radiograph is nonspecific, with findings of small bibasilar pleural effusions, and the patient's shortness of breath is unexplained. There is no evidence of an infiltrate in the right middle lobe (a) or Hampton hump (b), which is a peripheral wedge- or dome-shaped opacity with its base against the pleural surface. The diaphragms are not flat and the retrosternal airspace is normal, so (c) is incorrect.

Given these findings, congestive heart failure is an important consideration. In the Breathing Not Properly study, 47% of patients presenting to the emergency department with unexplained shortness of breath had congestive heart failure.[1] Unfortunately, chest radiography is not a sensitive test for congestive heart failure. The most useful finding on chest radiography is absence of cardiomegaly (sensitivity 74%, negative likelihood ratio 0.33, negative predictive value about 75%).[2] Absence of an elevated jugular venous pressure (sensitivity 39%, negative likelihood ratio 0.66) or peripheral edema (sensitivity 51%, negative likelihood ratio 0.64) do not lower the likelihood of congestive heart failure substantially.[2] Therefore, despite the nonspecific chest radiograph and relatively normal physical examination, the two leading diagnoses are lymphangitic spread from breast cancer and congestive heart failure.

Is measuring plasma brain natriuretic peptide or N-terminal pro brain natriuretic peptide appropriate for this patient?

a. Measuring plasma brain (also known as B-type) natriuretic peptide (BNP) or N-terminal pro BNP (NT-proBNP) is not appropriate because the tests are not specific for the diagnosis of congestive heart failure.
b. Because BNP testing takes many days, it is not useful in the acute setting.
c. Guidelines strongly recommend measuring BNP or NT-proBNP to exclude the diagnosis of congestive heart failure.
d. BNP testing is still experimental and not widely supported by evidence.

A normal BNP or N-terminal proBNP makes congestive heart failure unlikely, so (c) is the best answer. Very high levels of BNP or NT-proBNP, commonly available tests in Canada, strongly support the diagnosis of congestive heart failure, so (a) and (b) are not correct.[3] Over the last 15 years, substantial evidence has accumulated to support the use of natriuretic peptides in heart failure in a variety of settings, which makes (d) false.

Natriuretic peptides are the gold standard diagnostic biomarker of heart failure. Brain natriuretic peptide is produced as a precursor prohormone cleaved into BNP and NT-proBNP. Natriuretic peptides are released in response to myocardial stretch from volume or pressure overload, mainly from ventricular myocytes.[4] The Canadian Cardiovascular Society and the current American College of Cardiology/American Heart Association guidelines on heart failure recommend measuring BNP or NT-proBNP to support clinical judgment for the diagnosis of acute heart failure, particularly when the diagnosis of heart failure is uncertain (class 1, level of evidence A).[3,5]

This patient's BNP level was 1680 pg/mL. How should this finding be interpreted?

a. A plasma BNP level of 100 pg/mL or less rules out the diagnosis of heart failure.
b. A plasma BNP level of 500 or greater is indeterminate and requires confirmation with an NT-proBNP assay.
c. BNP cut-off points are different depending on race and sex, so more information is needed.
d. A plasma BNP level greater than 100 pg/mL rules in the diagnosis of heart failure.

The correct answer is (a). A plasma BNP level of 100 pg/mL or less (sensitivity 95%, specificity 63%, negative likelihood ratio 0.08, negative predictive value 93%), or an NT-proBNP level of 300 pg/mL or less (sensitivity 99%, specificity 43%, negative likelihood ratio 0.02, negative predictive value 98%), make congestive heart failure unlikely.[3,6] Conversely, a plasma BNP level of 500 pg/mL or greater supports the diagnosis of congestive heart failure. Confirmation with NT-proBNP is not required, and BNP cut-off points do not differ based on race or sex, so answers (b) and (c) are incorrect. A BNP level of greater than 100 does not rule in congestive heart failure. In 20% of patients with undifferentiated shortness of breath, BNP values are in the intermediate zone (BNP 100–499 pg/mL), where the diagnosis of heart failure cannot be ruled in or out,[7] so answer (d) is incorrect. We have summarized the accuracy of BNP and NT-proBNP in Box 1; the NT-proBNP cut-off values for ruling in congestive heart failure are age-specific.

In light of her ongoing shortness of breath, the patient had a bronchoscopy to rule out lymphangitic spread and an infectious cause; the bronchoscopy findings were negative for either cause. She was admitted to the internal medicine service for further evaluation of the unexplained dyspnea and high BNP levels. She improved substantially after diuretic therapy. Transthoracic echocardiography showed global reduced systolic function with an estimated left ventricular ejection fraction of 35%. In light of the patient's history of hypertension and slightly elevated troponin level, coronary computed tomography angiography was

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Box 1: Threshold values for the diagnosis of congestive heart failure based on natriuretic peptides[1,2]

B-type natriuretic peptide (BNP)

Heart failure unlikely (negative predictive value > 90%)
- Any age: ≤ 100 pg/mL

Heart failure likely
- Any age: ≥ 500 pg/mL
- < 50 yr: ≥ 450 pg/mL

N-terminal proBNP

Heart failure unlikely (negative predictive value > 90%)
- Any age: ≤ 900 pg/mL

Heart failure likely
- 50–75 yr: ≥ 500 pg/mL
- > 75 yr: ≥ 1800 pg/mL

performed, which did not show coronary artery disease. The final diagnosis was presumed nonischemic dilated cardiomyopathy, with anthracycline toxicity as the leading cause.

The patient's nonischemic cardiomyopathy was managed with diuretics and guideline-directed medical therapy.[5] She was counselled about the importance of fluid and salt restriction. The patient was discharged from hospital and followed in the heart function clinic.

In the ambulatory setting, would titrating heart failure therapy to a target BNP level improve clinical outcomes in this patient?

a. The patient should be given diuretics until the BNP level is less than 100 pg/mL.

b. A strategy of titrating heart failure therapy to a target BNP level is no more effective than usual care.

c. Titrating heart failure therapy to a target BNP level reduces hospital admissions and cardiovascular death.

d. Only patients with elevated BNP levels benefit from guideline-directed medical therapy.

The correct answer is (b); answer (c) is incorrect. The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial, the largest trial on the effect of titrating heart failure therapy to target BNP levels, showed no effect of titrating therapy to a target NT-proBNP of less than 1000 pg/mL on length of time to first hospital admission for heart failure or cardiovascular mortality, with a hazard ratio of 0.98 (95% confidence interval 0.79–1.22).[8] The study was stopped early because of futility. Diuretics alone should not be used to reduce natriuretic peptides; answer (a) is therefore incorrect. Answer (d) is also incorrect, as all patients who have chronic heart failure with reduced ejection fraction, regardless of BNP levels, should receive guideline-directed medical therapy, as outlined in the recent updated Canadian Cardiovascular Society guideline (class I, level of evidence A).[9]

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