

Case 4 - A 78-Year-Old Obese Woman with Sudden-Onset Dyspnea

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A 78-year-old woman sought medical attention for severe dyspnea. She had morbid obesity, hypothyroidism, and long-standing hypertension, and was taking captopril 150 mg, furosemide 40 mg, digoxin 0.25 mg, and levothyroxine 75µg daily.

For a long time she had dyspnea on heavy exertion, which became worse during the previous week, progressing to dyspnea at rest, orthopnea, nonproductive cough, and lower extremity edema. The patient had been diagnosed with heart failure at another medical institution. She was then medicated and discharged from hospital; nevertheless, her dyspnea worsened, and she sought emergency care at InCor.

Physical examination (April 28, 2007) revealed tachypnea (36 breaths/min), heart rate of 120 bpm, blood pressure of 150/80 mm Hg, and body mass index of 46,9 kg/m². She weighed 275.5 pounds and was 5 feet and 3 inches tall. Chest auscultation revealed bilateral rales in the lower lung fields and occasional wheezing. Examinations of the heart and abdomen were unremarkable. Bilateral lower-extremity edema was noted, greater in the right leg. Oxygen saturation (measured percutaneously) was 88%.

Laboratory data were as follows: urea 85 mg/dL, creatinine 1.8 mg/dL, blood glucose 116 mg/dL, hemoglobin 18 g/dL, hematocrit 57%, platelet count 228,000/mm³, troponin 2.8 ng/ml, CK-MB 10.8 µg/L, fibrin D-dimer > 5000 µg; and activated partial thromboplastin time (APTT) ratio 1.41.

The electrocardiogram (ECG) showed sinus rhythm with a heart rate of 114 bpm, PR interval of 175 msec, QRS duration of 94 msec, QT interval of 282 msec, QRS axis +150 oriented posteriorly, S₁Q₃T₃ pattern, and right bundle branch block (Figure 1).

The echocardiogram yielded the following measurements: aortic diameter of 32 mm, left atrial diameter of 32 mm, interventricular septal thickness of 10 mm and free wall thickness of 9 mm. The right atrium was markedly dilated, and the right ventricle was dilated and hypokinetic, with a systolic pressure of 85 mm Hg. The left ventricle was found to be normal.

Key Words:

Obesity; dyspnea; hypertrophy, ventricular.

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The diagnosis of pulmonary thromboembolism was proposed, and furosemide, 40 mg IV, was prescribed. The patient became hemodynamically unstable, requiring intravenous dopamine and orotracheal intubation for ventilatory support. Two hours of intravenous thrombolysis was performed with 100 mg of recombinant tissue plasminogen activator (rTPA).

On the night of the day after admission she went into cardiorespiratory arrest with pulseless electrical activity and died despite resuscitative efforts.

Clinical features

This is the case of a 78-year-old obese female patient with hypothyroidism, hypertension, and dyspnea on heavy exertion of one year duration that had progressed to dyspnea at rest during the previous week, associated with orthopnea, nonproductive cough, and lower-extremity edema.

Dyspnea is a symptom that results from the processing of multiple stimuli by the body¹. It may therefore differ from patient to patient, making an accurate diagnosis more challenging when assessed separately. A wide range of differential diagnoses, highly variable in severity, should be considered in a patient with dyspnea, including cardiac, pulmonary, neurological, muscular and even psychogenic causes². A thorough and detailed clinical examination, followed by appropriate selection and accurate interpretation of ancillary tests, may lead to the correct diagnosis. Even in the presence of obesity, which notoriously makes physical examination more difficult³, clinical symptoms play a decisive role in the differential diagnosis.

Dyspnea of cardiac origin is a clinical expression of pulmonary venous and capillary hypertension. In the case described herein, the abnormal findings on chest auscultation probably prompted the diagnosis of heart failure made at another institution. The presence of systemic hypertension, grade III obesity (BMI > 40 kg/m²), and chronic dyspnea on heavy exertion supports the hypothesis of heart failure, either systolic or diastolic, the latter being more common in elderly, obese⁴, and female patients, as was the case in this patient. Nevertheless, in the absence of triggering factors, such as acute myocardial infarction or acute valvular dysfunction, the clinical course of heart failure is generally slow and progressive. The patient's condition worsened relatively quickly over a one-week period, which argues against the diagnosis of heart failure.

The presence of chronic dyspnea on heavy exertion associated with polycythemia suggests that the patient had chronic hypoxemia. Among the differential diagnoses to be considered is obstructive sleep apnea syndrome, which is common in obese patients. In this condition, the patient's muscle tone is incapable of maintaining upper airway patency

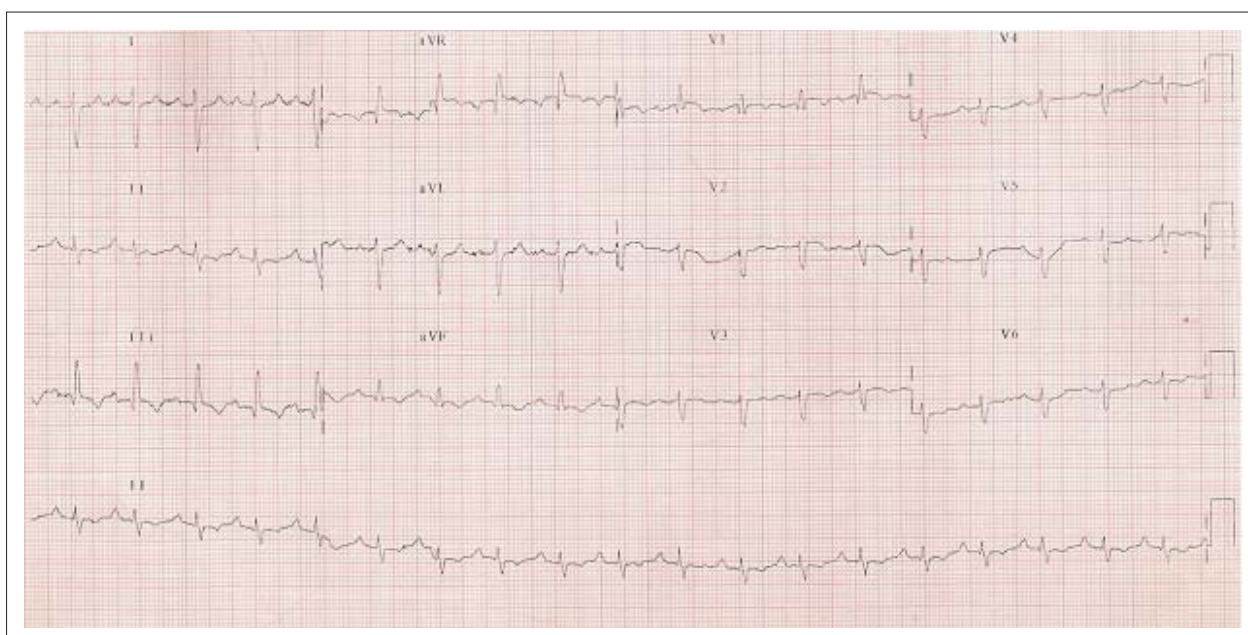


Figure 1 – ECG - sinus tachycardia, right bundle branch block, right axis deviation, and a $S_1Q_3T_3$ pattern.

during sleep, resulting in hypoventilation and hypoxemia, which leads to pulmonary hypertension, polycythemia and ultimately to heart failure, particularly right-sided heart failure, and impaired functional capacity⁵. A number of other conditions can also cause pulmonary hypertension, such as chronic obstructive pulmonary disease (COPD), chronic pulmonary thromboembolism, congenital heart diseases, and schistosomiasis, among others.

The presence of asymmetrical lower-extremity edema together with dyspnea and hypoxemia led us to the diagnosis of acute pulmonary thromboembolism (PTE). Even though PTE is associated with a broad spectrum of clinical syndromes, they can be divided into three major groups⁶: (1) pulmonary infarction, characterized by pleuritic pain and hemoptysis, (2) isolated dyspnea, which appeared to be the initial clinical presentation of our patient, and (3) circulatory collapse, defined as loss of consciousness or systolic blood pressure less than 90 mm Hg. Lung examination is abnormal in 29% to 37% of the patients with PTE, depending on whether or not prior cardiopulmonary disease is present⁷. Fifteen-day mortality rates in patients with isolated dyspnea and circulatory collapse (6.2% e 6.5%, respectively) are higher than those found in patients with pulmonary infarction (2.5%)⁸.

Venous thromboembolism (VTE) results from an imbalance in the coagulation system. The cardinal factors that contribute to intravascular coagulation have been known for more than a century, being originally described as a triad by Rudolf Virchow⁹ as follows: (1) endothelial injury, (2) hypercoagulability, and (3) blood stasis. These risk factors may be primary (inherited) or secondary (acquired) in nature.

The secondary risk factors are the most frequently found and thus more easily identified, such as prolonged immobilization, surgery in the previous three months, stroke, and malignancy¹⁰.

However, in some cases, known as idiopathic or primary venous thromboembolism, these risk factors are not present. Under these circumstances, particular attention must be given to the investigation of genetic factors. The most common genetic defect in these patients is a mutation in factor V Leiden, accounting for up to 40% of the cases¹¹. The patient described herein was obese and hypertensive, and both conditions are major risk factors for venous thromboembolism in women¹².

Her oxygen saturation, measured by percutaneous oximetry, was 88%. Such hypoxia associated with tachypnea (36 breaths/min) and tachycardia (120 bpm) reflects both the presence of respiratory failure and severity of the clinical picture. Hypoxemia in PTE may be explained by numerous mechanisms, the most important of which are changes in the pulmonary ventilation-perfusion ratio. While the presence of hypoxemia is not helpful in establishing the diagnosis¹³, it plays a key role as a predictor of death. Pulse oximetry, widely available in emergency departments, is a quick and easy-to-perform test. Even in patients who initially are neither hypotensive nor requiring mechanical ventilation, a pulse oximetry reading < 95% at hospital admission is associated with greater 30-day mortality (20% compared with only 2% in patients with pulse oximetry \geq 95%)¹⁴.

The patient's ECG showed sinus tachycardia, right axis deviation and a $S_1Q_3T_3$ pattern. This pattern is traditionally considered as suggestive of pulmonary embolism, and for decades has been known to reflect acute *cor pulmonale*¹⁵.

Care must be taken when interpreting this electrocardiogram. The $S_1Q_3T_3$ pattern is not specific for PTE, occurring in 13.5% of the patients in whom this diagnosis was initially suspected but subsequently ruled out¹⁶. Its absence is not sufficient to exclude the diagnosis either, because of its low sensitivity. The $S_1Q_3T_3$ pattern is found in only 11.6% of PTE patients¹⁶.

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The electrocardiogram may be completely normal in patients with PTE, the most common rhythm disturbance being sinus tachycardia, which pathophysiologically reflects an increase in cardiac output to improve oxygen delivery¹⁷.

Plasma fibrin D-dimer was $> 5000 \mu\text{g}$, an elevated level that shows activation of the endogenous fibrinolytic system, since D-dimer is a fibrin degradation product. Its use in the diagnosis of PTE has been extensively studied. The D-dimer assay has high sensitivity and negative predictive value but poor specificity¹⁸. Therefore, it is best used to exclude the diagnosis of PTE in patients with low or intermediate probability. Plasma D-dimer levels are elevated postoperatively and in patients with acute myocardial infarction, sepsis, malignancies, and other systemic diseases.

This patient showed increased CK-MB and troponin levels, which initially could suggest acute myocardial infarction. Although cardiac troponins have been shown to be highly specific markers of myocardial injury, we must bear in mind that an elevation in serum levels of troponin does not mean that the mechanism of such elevation was atherosclerotic plaque instability, which is found in AMI patients. It is known that troponin elevation may be secondary to acute right ventricular overload, with increased metabolic demand and thereby ischemia¹⁹; this may have been the mechanism of troponin elevation in our patient. Kinetics of troponin release may be useful in the differential diagnosis between acute myocardial infarction and PTE, since in the latter condition troponin serum levels usually return to normal levels within the first 40 hours, unlike in acute myocardial infarction²⁰. Elevated levels of cardiac troponin have proven to be of prognostic value in patients with PTE. Mortality rates are substantially higher in patients with high troponin levels than in those with normal levels (19.7% and 3.7%, respectively)²¹. Even in a subgroup of hemodynamically stable patients, elevated troponin levels were associated with a mortality rate 5.9 times higher²¹.

The echocardiogram confirmed the suspicion raised by clinical and electrocardiographic findings, together with elevated troponin levels, severe pulmonary hypertension, and right ventricular overload. Pulmonary artery systolic pressure was 85 mm Hg, and the right ventricle was dilated and hypokinetic. The echocardiogram also showed normal left ventricular function, an important finding as it rules out heart failure, either systolic or diastolic, as the cause of the patient's clinical condition. Only 40% of PTE patients have suggestive changes on echocardiogram, but if present these changes are helpful in establishing the presumptive diagnosis and constitute an excellent prognostic tool²². Mortality rates are twice as high in patients with right ventricular hypokinesis as in those without hypokinesis²².

The diagnosis of pulmonary thromboembolism is difficult. It is usually based on the clinical probability of each patient, followed by identification of the thrombus or its reperfusion in lung perfusion imaging. A number of diagnostic algorithms for PTE have been proposed, but none has offered substantial benefit over the others²³. Their differences are based primarily on the availability of the ancillary test chosen and the experience of each institution with it.

Scores were created in an attempt to standardize the risk stratification of PTE. The most widely used are those developed by Geneva and Wells, both of which are very helpful and share operating characteristics²⁴. The modified Wells criteria include clinical signs of deep venous thrombosis, absence of a more likely diagnosis than PTE, tachycardia, prolonged immobilization, previous thrombotic event, hemoptysis, and malignancy²⁵. After clinical stratification, if suspicion of PTE still remains it should be confirmed by diagnostic imaging using two main strategies. One of them is helical CT pulmonary angiography, which may confirm the diagnosis and has been the method of choice of centers experienced with this technique. Despite the disadvantage of using iodinated contrast medium, it has sufficient sensitivity to safely exclude the diagnosis of clinically significant pulmonary embolism²⁵. The second strategy is based on ventilation/perfusion lung scans, which can confirm the diagnosis of PTE in patients with high clinical probability. However, in some patients invasive pulmonary angiography is needed to rule out the disease¹⁰. Lower-extremity venous Doppler ultrasound may also be used, and has sufficient diagnostic sensitivity for patients in whom therapies associated with greater morbidity, such as thrombolysis or surgery, will not be considered²⁶.

The patient progressed to hemodynamic instability, requiring intravenous dopamine and orotracheal intubation for ventilatory support.

The shock associated with pulmonary thromboembolism results from right ventricular dilation and dysfunction, with a reduction in cardiac output associated with a leftward shift of the interventricular septum, thereby decreasing LV preload and output.

This causes both a decrease in coronary perfusion and right ventricular ischemia, further impairing RV function and creating a vicious circle that ultimately leads to tissue hypoperfusion⁴.

At that point, we were faced with an extremely difficult clinical decision. There was no time to make a definite diagnosis of PTE, which could have been obtained using imaging studies. The patient's clinical instability did not allow any ancillary test to be made outside the confines of the intensive care unit, hence the presumptive diagnosis of PTE, which was based mostly on clinical and echocardiographic findings. A fibrinolytic agent was then administered.

The aim of the fibrinolytic therapy was threefold: to improve RV dysfunction by dissolving the thrombus and thus reduce pulmonary arterial obstruction; to prevent the continuous release of serotonin and other neurohumoral factors that may exacerbate pulmonary hypertension; and perhaps to dissolve thrombi in other sites, such as lower extremities and the pelvic region. It is especially indicated for patients with massive or submassive pulmonary thromboembolism. The fibrinolytic approved by the FDA was t-PA (Alteplase) 100 mg, in continuous infusion, followed by heparinization²⁶. Patients considered for fibrinolytic therapy should be assessed for contraindications, because the mean incidence of intracranial hemorrhage is 3%. Although fibrinolysis is considered one of the first choices in patients with massive PTE, its actual clinical benefit remains unclear. A review of clinical trials found no

reduction in 90-day mortality and recurrence of pulmonary thromboembolism¹³. In patients with massive or submassive PTE in whom fibrinolysis is contraindicated or failed, surgical or catheter embolectomy must be considered²⁶.

On the night of hospital day 2 the patient went into cardiorespiratory arrest with pulseless electrical activity, which may have been due to pulmonary thromboembolism, myocardial ischemia, hypoxia, electrolyte disorders (hypo- and hyperkalemia), hypovolemia, acidosis, or hypothermia. The cardiorespiratory arrest was refractory to cardiopulmonary cerebral resuscitation.

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Diagnostic hypothesis - acute massive pulmonary thromboembolism

Other diagnoses - morbid obesity, hypertension, hypothyroidism

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Autopsy

Postmortem examination showed a severely obese woman. The heart weighed 640 g and showed biventricular hypertrophy, greater in the right ventricle, which was slightly dilated.

The pulmonary artery was dilated, and a fresh, massive, bilateral pulmonary thromboembolism was found occluding first-generation branches of the left and right pulmonary arteries at the hilar level (Figure 3). Histological examination of several organs confirmed the above findings and showed in the thyroid gland, which was normal in size and not adhered to neighboring structures, a severe lymphocytic inflammatory infiltrate, without formation of lymphoid follicles, accompanied by fibrosis (Figure 4). The kidneys were found to have a finely granular surface, hyaline arteriosclerosis, plus rare foci of interstitial fibrosis and glomerulosclerosis. The gallbladder was small and contained a single large stone. The aorta was mildly atherosclerotic. No internal genital organs were found (probably due to prior radical hysterectomy).

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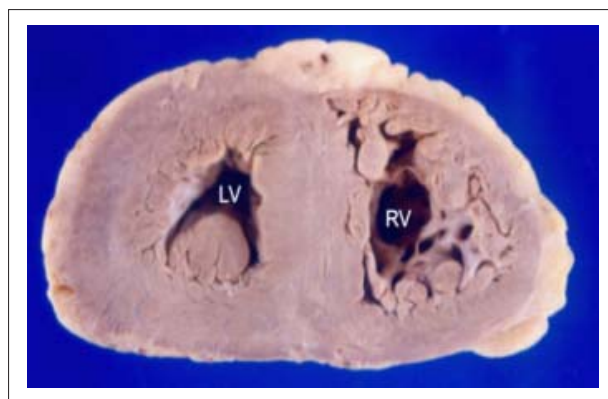


Figure 2 - Cross-section of the heart showing left ventricular (LV) and right ventricular (RV) hypertrophy, greater in the latter.

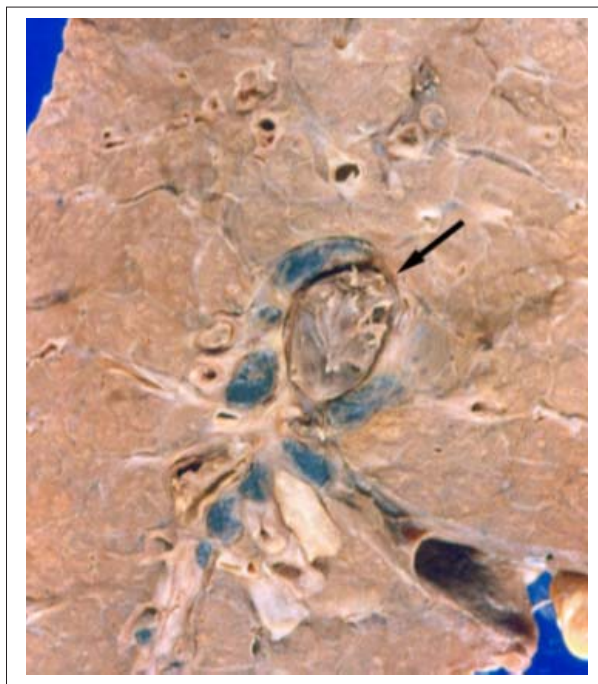


Figure 3 - Longitudinal section of the right lung at the hilar level showing occlusion of the pulmonary artery by a fresh thrombus (arrow).

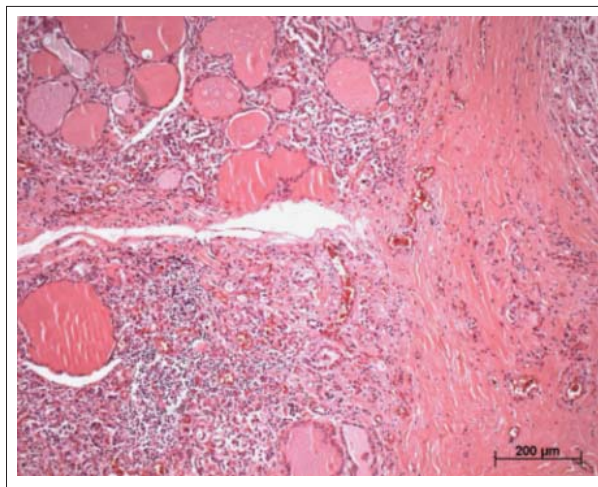


Figure 4 - Cross-section of the thyroid gland showing the presence of mononuclear inflammatory cell infiltrate, fibrosis, and atrophy of thyroid follicles, characterizing chronic lymphocytic thyroiditis. There are no lymphoid follicles. Hematoxylin-eosin staining.

Pathologic Diagnoses

Morbid obesity; right and left ventricular hypertrophy; chronic lymphocytic thyroiditis; chronic calculous cholecystitis; and acute massive pulmonary thromboembolism (cause of death).

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Comments

We report a case of a 78-year-old woman with hypertension, hypothyroidism, and morbid obesity. Postmortem examination

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revealed not only mild left ventricular hypertrophy, which could be explained by systemic hypertension, but also moderate right ventricular hypertrophy. The latter is most probably due to chronic pulmonary hypoventilation and/or obstructive sleep apnea secondary to morbid obesity, which may cause chronic pulmonary hypertension and right ventricular overload²⁷. It is important to note that in addition to right ventricular hypertrophy, other changes in this case are closely related to severe obesity, such as gallstones, the systemic hypertension itself, and pulmonary thromboembolism^{28,29}.

Therefore, we believe that morbid obesity was the

primary disease of the patient.

The morphological change found in the thyroid gland, that is, chronic lymphocytic thyroiditis, may explain the thyroid dysfunction. Indeed, hypothyroidism (either clinical or subclinical) is also associated with morbid obesity, and is found in 19.5% of the patients³⁰.

Interestingly, even though hypothyroidism has been traditionally considered as one of the causes of obesity, no consensus exists on the actual causal relationship between both entities³¹.

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