TUTORIAL

Pregabalin-associated Pulmonary Thromboembolism

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Abstract

Pregabalin is a commonly prescribed medicine for the treatment of diabetic neuropathy. The adverse effect of this drug on long-term use remains unknown. This is a case of a 47-year-old female who presented to hospital with a history of shortness of breath. She was a known case of with diabetic neuropathy receiving pregabalin 75 mg orally once a day. The patient had a heart rate of 112 beats/minute, blood pressure of 102/52 mm Hg, respiratory rate of 28/minute, peripheral oxygenation saturation of 88% on room air, and D-dimer of 2.29 mg/L. Transthoracic echocardiography [two-dimensional (2D)] showed paradoxical motion of intraventricular septum (IVS), elevation in pulmonary artery systolic pressure (50 mm Hg), mild right atrial/right ventricular (RA/RV) dilatation and normal left ventricular (LV) systolic function. Chest X-ray suggestive of left middle zone haziness. Computed tomography of pulmonary angiogram (CTPA) showed a thrombus at the left main pulmonary artery. The other risk factors for pulmonary embolism (PE) were absent. Hence, a diagnosis of acute pulmonary thromboembolism (PTE) secondary to drug-induced (pregabalin) was made and managed with tenecteplase, heparin, and later rivaroxaban. The patient improved and was discharged home in hemodynamically stable condition. This case report highlights a case of pregabalin-associated PTE. Early diagnosis and management can reduce morbidity and mortality.

Keywords: Breathlessness, Neuropathy, Pregabalin, Pulmonary thromboembolism.

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Introduction

Pulmonary thromboembolism (PTE) is a life-threatening condition. Since the presentation of PTE is nonspecific, the diagnosis is a major challenge. Pregabalin-associated cardiovascular side effect such as pulmonary embolism (PE) is possible but a rare phenomenon.[1] The breathing issues associated with pregabalin (increased pauses in breathing during sleep) have been warned by the United States Food and Drug Administration in the year 2019.[2] This writeup reports pregabalin-associated PTE due to long-term pregabalin treatment for diabetic neuropathy. The clinician should have a high degree of suspicion about PE in patients who present to the hospital for breathlessness and on long-term pregabalin treatment.

Case Description

This is a case of 47-year-old female who presented to a tertiary care center with a history of shortness of breath for 4 days. Breathlessness was sudden in onset and associated with on/off chest pain and dry cough. She also complained of intermittent pain in both lower limbs. She was a known case of diabetes mellitus (oral metformin 250 mg once daily) and hypertensive (oral metoprolol 50 mg once daily). She was also on tablet pregabalin 75 mg once daily for diabetic neuropathy for 5 years. Initially evaluated in the emergency department (ED), she was afebrile with a heart rate of 112 beats/minute, blood pressure of 102/52 mm Hg, respiratory rate of 28/minute, and a peripheral oxygenation saturation of 88% breathing room air. Routine blood investigations showed hypokalemia with potassium 3.0 mEq/L, hyponatremia with sodium 126 mEq/L, serum creatinine 0.4 mg/dL, hemoglobin 8.7 gm/dL, total leukocyte count of 18,000, prothrombin time of 13.1 seconds, international normalized ratio (INR) of 0.9, Activated partial thromboplastin time (APTT): 25.3, troponin test < 40, NT-Pro brain natriuretic peptide (BNP) of 1774, and D-dimer of 2.29 mg/L. An electrocardiogram (ECG) showed T-wave inversion in lead III. Echocardiography showed paradoxical motion of the interventricular septum (IVS), elevated pulmonary artery systolic pressure (50 mm Hg), mild right atrial/right ventricular (RA/RV) dilatation, and normal left ventricular (LV) systolic function. Chest X-ray revealed left middle zone haziness/consolidation (Fig. 1). Lower limb Doppler study on both sides was normal. Ultrasound of the abdomen was suggestive of grade I fatty changes in the liver. The patient was initially managed with potassium correction, one unit blood transfusion, parenteral iron, intravenous frusemide, airway-nebulization, and supportive care. Additionally, she received oseltamivir and azithromycin considering community-acquired pneumonia. Computed tomography of pulmonary angiogram (CTPA) showed dilatation of the main pulmonary artery trunk, filling defects in the left main pulmonary artery causing near complete occlusion, suggestive of acute thrombus (Fig. 2). Risk factors such as bedridden status, trauma, thrombophilia, local infection, venous compression, intravenous catheters, cancer, oral contraceptives, and pregnancy was ruled out. The thrombotic workup namely antithrombin-III assay, homocysteine, protein-C,

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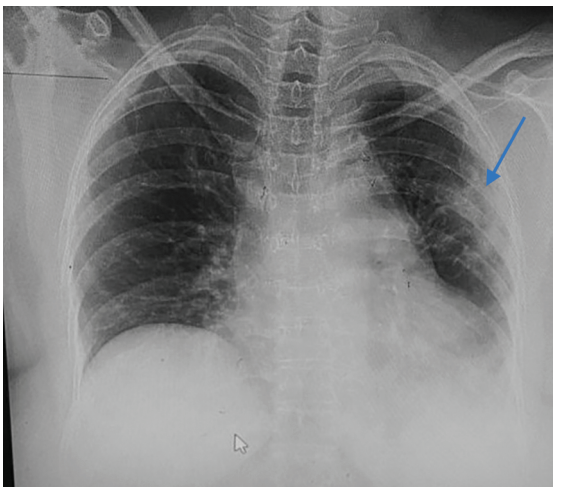

Fig. 1: Chest X-ray of the patient showing left middle lobe haziness

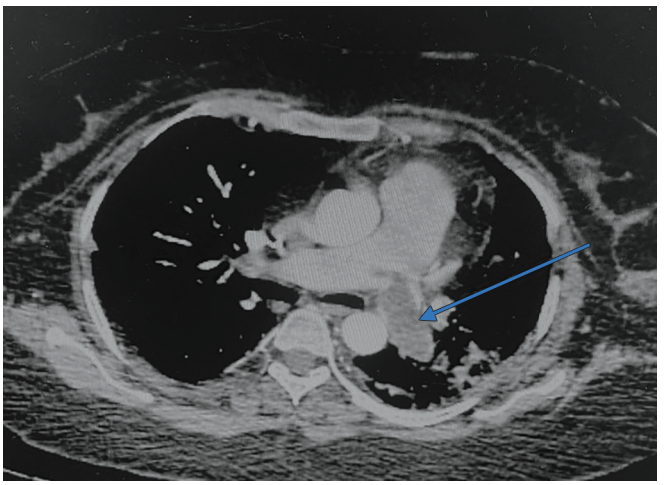

Fig. 2: Contrast-enhanced computed tomography of thorax showing thrombus obstructing left main pulmonary artery

and protein-S assay were normal. Since this patient did not exhibit multiple arterial, venous, or small vessel thrombosis nor did she have a history of multiple embryonic losses, premature birth, or fetal death, antiphospholipid antibody syndrome was not considered. A diagnosis of acute PTE was considered probably secondary to long-term use of pregabalin. She was thrombolysis with tenecteplase (intravenous, 40 mg) after following the fibrinolytic checklist. Subsequently, intravenous heparin infusion was initiated. She improved dramatically with a resolution of hypotension, tachycardia, and hypoxia. Heparin was changed to oral rivaroxaban and the patient was shifted to wards on the 4th day and later discharged home on the 6th day in hemodynamically stable condition.

Discussion

Pregabalin is a gabapentinoid, first synthesized by chemist Richard Bruce Silverman in the year 1990.[3] Pregabalin is a γ-aminobutyric acid (GABA) analog, acts as an inhibitor of $\alpha_2\delta$ subunit of voltage-dependent calcium channels.[4,5] It indirectly increases the GABA levels in the brain through the dose-dependent expression of GABA synthesizing enzyme l-glutamic acid decarboxylase.[6,7] On oral administration it is absorbed from the intestine through large neutral amino acid transporter 1 (LAT-1). Pregabalin can cross the blood–brain barrier (BBB) as the LAT-1 is highly expressed at BBB.[8,9] Pregabalin has a half-life of 6.3 hours and is excreted in urine unchanged[10] and is mainly used for the treatment of neuropathic pain secondary to diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain.[11] It is also used in drug-resistant focal epilepsy, anxiety disorder, posttraumatic stress disorder, bipolar disorder, and migraines.[12] Side effects of pregabalin use are mainly drowsiness, dizziness, ataxia, vertigo, memory impairment, fatigue, and constipation. Rhabdomyolysis, neutropenia, hypotension, pancreatitis, dysphagia, thrombus formation, and first-degree heart block are very rare side effects. Pan et al. conducted a retrospective cohort study to look for cardiovascular risk in patients who were prescribed gabapentin and pregabalin for the treatment of diabetic neuropathy.[1] In patients who were prescribed pregabalin, they found a higher incidence of deep vein thrombosis (DVT), myocardial infarction, PE, and stroke. Even some case reports have highlighted pregabalin and gabapentin-related heart failure.[13] They concluded that the high-risk of cardiovascular events is probably due to fluid retention secondary to altered myogenic tone. The fluid retention causes increased cardiac output/blood pressure. This leads to increased turbulence causing endothelial damage; and hence, a high incidence of cardiovascular events. Our patient was on pregabalin treatment for diabetic neuropathy for 5 years.

Pulmonary embolism (PE) is defined as the obstruction of the pulmonary artery secondary to thrombus resulting in reduced blood flow distal to the obstruction. The incidence is about 60–120 cases/100,000 population/year.[14] Around 80% of times the thrombus comes from deep veins of the lower limbs and pelvis and around 6% of it comes from the upper limbs.[15,16] Risk factors include older age, bedridden status, trauma, thrombophilia, local infection, venous compression, intravenous catheters, cancer, oral contraceptives, and pregnancy.[17] Our patient did not have any risk factors for PE. The pulmonary thromboembolism may be due to migration of thrombus from the deep vein of the leg (though the bilateral lower limb doppler was normal). Clinical presentation varies according to the site and size of the thrombus occluding the lung. Patients can be asymptomatic and detected on chest imaging done for other diagnostic evaluation[18] or they can present with severe hypoxia, hemodynamic instability, and death. Common clinical features include breathlessness, chest pain, tachycardia, normal or low blood pressure, hypoxia, hemoptysis, leg pain, and unexplained syncope.[19] Our patient had breathlessness with a slight drop in blood pressure and saturation.

Diagnosis is based on clinical features, risk factors, D-dimer, and radiological investigations. D-dimer is a fibrin degradation protein that is increased in case of thrombus formation. It has a negative predictive value of 70–100%.[20,21] Few scoring systems (Well's score and revised Geneva score) have been proposed to stratify patients as having a low, moderate, or high probability for PE.[22,23] They include components such as unilateral leg swelling, surgery, heart rate > 99 bpm, hemoptysis, age > 49 years, and previous DVT. The Well's score is 0–8 points. Up to 4 points, the patient is considered to have a low probability of PE (<15%), 5–6 is considered intermediate, and 7–8 is considered a high probability of PE (>40%). Our patient had a score of 1 which is of low probability for PE. Other investigation includes CTPA, ventilation/perfusion lung scintigraphy (V/Q scan), two-dimensional (2D) echocardiography, and chest X-ray. The treatment of PE depends upon the risk of inhospital mortality.[24] The inhospital risk is calculated based on the simplified PE severity index (sPESI). The sPESI score includes

six components with 1 score each [age > 80 years, heart rate > 109 bpm, systolic blood pressure (SBP) < 100 mm Hg, oxygen saturation on room air < 90%, chronic cardiopulmonary disease, and cancer]. Patients with hemodynamic instability should be managed in the intensive care unit with thrombolytic therapy.[25] Since our patient had a score of 2 and had hemodynamic instability hence, she was thrombolysis with tenecteplase. Surgical embolectomy or catheter-based thrombus aspiration should be tried in patients who have contraindications for thrombolysis treatment. Inferior vena cava (IVC) filters are used in case of recurrent PE.[26] Venoarterial extracorporeal membrane oxygenator can be used in case of cardiac arrest.[27]

The optimal duration of treatment with anticoagulation remains unclear. The trials comparing 3 vs 6 months' treatment with vitamin-K antagonists did not show much difference in PE recurrence.[28] The extended course of treatment is considered in patients with a family history of venous thromboembolism and cancer.

Tutorial on Pulmonary Embolism

What is the Incidence of Pulmonary Embolism?

The overall incidence of PE is about 2.81/100,000 population. The incidence increases with increasing age and it is higher in males compared to females.

What are the Risk Factors for Pulmonary Embolism?

The risk factors for PE are either genetic (mutation in factor V Leiden and prothrombin gene) or acquired (prolonged immobilization, bedridden status, surgery, trauma, malignancy, oral contraceptives, pregnancy, chronic smoking, obesity, and drugs).

What are the Hemodynamic Consequences of Pulmonary Embolism?

Hemodynamic consequences include tachycardia, syncope, arrhythmias, and hypotension (due to reduced stroke volume, decreased left ventricle preload, and cardiac output).

What is the Spectrum of Clinical Presentation?

The diagnosis of PE based on clinical features is challenging because its presentation is nonspecific. Usually, patients present with breathing difficulty, chest pain, syncope, tachycardia, hypotension, arrhythmias, fever, hemoptysis, calf pain/edema, and sudden cardiac arrest.

Briefly Explain the Pathogenesis

The pathogenesis behind PE is mainly related to Virchow's triad (venous stasis, endothelial injury, and a hypercoagulable state). The thrombi occur usually from the lower extremity due to decreased blood flow and the presence of cusps and bifurcations.

What are the Common Presenting Symptoms of Pulmonary Embolism?

If the patient has acute obstruction of pulmonary vessels, then the symptoms are immediate, if it is subacute then they have symptoms for days to weeks. In case of chronic obstruction then they have symptoms over many years. If patients have massive PE, then there will be hemodynamic instability [systolic blood pressure (SBP) < 90 mm Hg/fall of SBP > 40 mm hg for 15 minutes/hypotension requiring inotropes or vasopressors]. If the thrombus presents at bifurcation or main pulmonary artery then there will be sudden onset of symptoms along with hemodynamic instability. The incidence of death is higher in these types of patients if not treated early. The presence of segmental or subsegmental thrombus usually leads to pulmonary infarction or pleuritis.

What are the Most Common Electrocardiogram Signs in Pulmonary Embolism?

In patients with PE, the most common ECG finding is tachycardia. The S1Q3T3 pattern in ECG is seen in <10% of patients. Other changes such as nonspecific ST-segment and T-wave changes, right bundle branch block, and atrial fibrillation are less common.

Briefly Explain the Scores of Predictions of Pulmonary Embolism

The scores of clinical probabilities are used to stratify patients as low, moderate, or high-risk of having PE. These scores include the Wells score, revised Geneva score, and PE rule-out criteria (PERC) system.

Wells system incorporates six criteria—clinically suspected DVT (3 points), heart rate > 100/minute (1.5 points), immobilization or surgery within the previous 4 weeks (1.5 points), previous DVT or PE (1.5 points), hemoptysis/cancer within 6 months (1 point), and alternative diagnosis is less likely (3 points). The clinical probability of PE is <15% if the score is 4.5 or less, 15–40% if the score is 5–6, and >40% if the score is >6.

The revised Geneva system includes six criteria—unilateral lower limb pain (3 points), pain on lower limb palpation and unilateral edema (4 points), heart rate 75–94/minute (3 points), heart rate > 94/minute (5 points), surgery or lower limb fracture within the previous 4 weeks (2 points), previous DVT or PE (3 points), hemoptysis (2 points) cancer within 12 months (2 points), age > 65 years (1 point). The clinical probability of PE is <15% if the score is 4 or less, 15–40% if the score is 5–10, and >40% if the score is >10.

The PERC system has six components unilateral leg swelling (1 point), heart rate >99/minute (1 point), immobilization or surgery in the previous 4 weeks (1 point), previous DVT or PE (1 point), hemoptysis (1 point), age > 49 years (1 point), oxygen saturation by pulse oximetry on room air <95% (1 point), and estrogen use (1 point). If the score is 0 then this score has 98.5% negative predictive value to rule out PE.

What is the Significance of D-dimer/Troponin and Brain Natriuretic Peptide in Pulmonary Embolism?

Whenever there is thrombus formation there will be more formation of fibrin which undergoes fibrinolysis to form D-dimer (fibrin degradation fragment). Increased in the presence of thrombosis. The normal value of D-dimer is 500 ng/mL. This D-dimer is often used as the negative predictive value to rule out PE. If patients have a low or intermediate probability for PE, then 500 ng/mL or less D-dimer almost rules out the presence of PE. Serum troponin-I and T levels are elevated in 30–50% of patients with moderate–large PE due to right ventricular dysfunction. These levels are helpful in prognosis rather than as a diagnostic marker. Increased levels of BNP/N-terminal (NT)—proBNP determines the right ventricular strain. Higher levels have a direct correlation with mortality.

What are the Chest X-ray Features of Pulmonary Embolism?

The X-ray features in PE are nonspecific. The presence of less common signs such as Hampton hump (hump-shaped opacity at the periphery of the lung), Westermark sign (the hypoperfusion of

the lung beyond the occlusion), and Palla sign (sausage appearance of descending pulmonary artery) should give the clue about PE. The patient can also have atelectasis and pleural effusion.

What are the Echocardiographic Features of Pulmonary Embolism?

Bedside echocardiography can show right atrium and right ventricular dilatation with flattened IVS. Sometimes we can see the thrombus between the heart and pulmonary artery.

What are the Other Imaging Modalities in Diagnosing Pulmonary Embolism?

The main imaging modality for the diagnosis of PE is CTPA. The V/Q scan is another modality to diagnose PE. It has a low sensitivity for diagnosing PE (55–98%). The more invasive diagnostic method is pulmonary angiography which is performed by passing a catheter into the pulmonary artery using fluoroscopy. The diagnostic ability is similar to CTPA.

What do You Understand by the Term Triple Ruleout on Computed Tomography?

Triple-rule-out CT angiography is an extended CT coronary angiogram. It is usually done in patients having atypical chest pain. It can rule out aortic dissection, PE, coronary artery disease, and nonvascular chest disease.

Briefly Explain about Pulmonary Embolism Severity Index Score

The PESI score is used to stratify the risk of inhospital mortality in patients having PE. It has six components age > 80 years (1 point), history of cancer (1 point), chronic cardiopulmonary disease (1 point), heart rate > 109/minute (1 point), SBP 100 mm Hg (1 point), and oxygen saturation by pulse oximetry on room air < 90% (1 point). A PESI score of 0 means a patient with PE is at low risk for early mortality. Some studies have shown that the PESI score of 0 had a 30-day mortality rate of 1%.

What are the Treatment Modalities for Pulmonary Embolism?

Before treating any PE patients, we need to stratify these patients based on PESI score as low, intermediate, or high-risk for inhospital mortality. If the PESI score is 0, they are considered low risk for early mortality; and hence, can be treated with low molecular weight heparin (LMWH) followed by vitamin K antagonists (warfarin). Some studies have shown a 30-day mortality of 1% in PESI 0 patients. Patients with a PESI score of 1 and SBP > 90 mm Hg are considered intermediate risk and their 30-day mortality was 10%. They should be treated with LMWH and direct oral anticoagulants (apixaban, rivaroxaban, and dabigatran) within 72 hours of LMWH. Patients with SBP < 90 mm Hg for >15 minutes and associated with end-organ hypoperfusion (acute kidney injury) have 30 days mortality of 20%. These patients should be treated with recombinant tissue plasminogen activators (streptokinase, tenecteplase). Those patients who have contraindications for thrombolysis should undergo either catheter-directed mechanical fragmentation/thrombus aspiration or surgical embolectomy. The duration of treatment using LMWH/direct oral anticoagulants remains unclear. In the case of unprovoked PE, the continuation of treatment for 3 or 6 months did not show much difference in PE recurrences. Patients having a family history of venous thromboembolism or cancer should be treated for an extended period of time.

Is there Any Role of the Inferior Vena Cava Filter?

An IVC filter is used when anticoagulation is contraindicated. It is also indicated when routine anticoagulation does not prevent the recurrence of PE. Many studies have shown that the use of IVC filters reduces the recurrence of PE but has no effect on mortality.

Briefly Explain about Wells Score for the Clinical Probability of DVT

Wells system incorporates six criteria—clinically suspected DVT (3 points), heart rate >100/minute (1.5 points), immobilization or surgery within the previous 4 weeks (1.5 points), previous DVT or PE (1.5 points), hemoptysis/cancer within 6 months (1 point), and alternative diagnosis is less likely (3 points). The clinical probability of PE is < 15% if the score is 4.5 or less, 15–40% if the score is 5–6, and >40% if the score is >6.

How do You Manage DVT?

If the patient has unprovoked DVT, they should be treated with direct oral anticoagulants. Thrombolytic therapy is not recommended. These uncomplicated DVTs can be managed at home rather than hospital admission. The primary treatment is for 6 months but for secondary prevention, the treatment should be continued for an indefinite duration. In case of provoked DVT (surgery, hormonal therapy, prolonged bed rest, and fractures), these patients should be treated with direct oral anticoagulants for 3–6 months. Long-term treatment for >6 months is not recommended.

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