

Diagnosis and Treatment of Pulmonary Embolism for Patients with Cancer: Better Outcomes Result from Earlier Detection

Nischal Chennuru^{1*} and Elizabeth Kwo²

¹Columbus, OH, USA

²Preventative Care and Occupational Medicine Physician, Harvard Medical School, Boston, USA

*Corresponding Author: Nischal Chennuru, Columbus, OH, USA

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Abstract

Risk of pulmonary embolism (PE) is relatively high in patients with malignancies. It can happen with any cancer and the incidence is further increased by treatment modalities including surgery, chemotherapy and radiation and is also affected by disease progression. Pulmonary embolism can manifest initially without symptoms but also occur as life-threatening cardiogenic shock. Diagnosis is usually confirmed by CT angiogram but algorithms to determine the pretest probability of PE using several noninvasive tests including D-dimer and EKGs, chest x-ray. Mortality of untreated pulmonary embolism is very high. Treatment of pulmonary embolism is dependent upon the symptoms and the burden of the clot which can vary from only anticoagulation to requiring thrombolytic therapy or surgical embolectomy.

Keywords: Pulmonary Embolism (PE); CT Angiogram; D-Dimer; EKGs, Chest X-Ray

Introduction

Pulmonary Embolism is one of the entity of venous thromboembolism. Venous Thromboembolism can present as Pulmonary Embolism or Deep vein thrombosis. The prevalence of malignancy in patients with pulmonary embolism ranges between 4% and 20%. Approximately fifty percent of patients with tumors have thromboses on autopsy. The overall risk of pulmonary embolism is increased by 20 - 30 fold in patients with tumors compared to general populations [2]. The risk of thromboembolic disease increases in patients with mutations of genes affecting the coagulation system, congenital vascular malformations and acquired hypercoagulable states. The most vital acquired factors are oral contraceptives, surgical treatment, hormone replacement therapy and cancer [1-3].

Individuals with active cancer who have undergone any surgery, particularly in the small pelvis or the abdominal cavity, are prone to 5 times higher risk of thromboembolism, which is affected by the active cancer; and also obesity, duration of surgery, length of recovery, radiotherapy and systemic therapy. Additionally, chemotherapy and hormone therapy can increase the risk of venous thrombosis.

Major risk factors influencing risks are advanced age, type of cancer and its stage, type of chemotherapy, cancer duration, cancer response to therapy such as progression, nutritional status, patient mobility, functional status and functional efficiency of liver and kidneys [1,3].

Whether or not thromboembolic disease is symptomatic, the occurrence in a cancerous patient is about 20% and the risk of death within 6 months is increased from 15% to 80% in cases of thromboembolism. It is the second cause of death among cancer patients [3].

The objective of this article is to review the risk factors of pulmonary embolisms and its implications and management in cancer patients.

Risk factors

Venous thrombosis in cancer patients is complicated and is multifactorial. Patient related factors include age, immobilization, smoking, Hyperlipidemia and Diabetes mellitus, history of previous thromboembolic episodes. Malignant cell related factors include the production of procoagulants by tumor cells, fibrinolytic and proaggregatory conditions caused by tumor, release of proinflammatory and pro-angiogenic cytokines and interaction with vascular endothelial cells and blood cells. Treatment related factors include surgery, chemotherapy, radiation and central venous catheters. vascular changes due to treatment. Complications include infections, heart failure, liver disease, renal disease and lung disease [2].

Clinical picture

PEs often have nonspecific clinical presentations, which can be difficult to diagnose. The typical symptoms are shortness of breath, chest pain, syncope, hemoptysis and cough. These symptoms may often be diagnosed instead as respiratory infections, cancer progression or complication of chemotherapy and radiotherapy due to similarity of symptoms.

A physical examination of the patient most often reveals tachycardia, tachypnea, and rarely auscultatory changes over lung fields. There may be features of right heart failure- increased jugular venous pressure in massive PE. Only 1/3 of patients have clinical signs of coexisting DVT. The clinical picture and course of acute PE depend on the number and size of the clot affecting the pulmonary arteries, and cardiorespiratory function. Occasionally the first presentation of PE can be sudden cardiac arrest, and rarely pulmonary edema.

The diagnosis of PE may be hindered by the presence of underlying lung diseases like bronchiectasis, emphysema, lung metastases and lung injury secondary to oncological treatment: radiotherapy and/or chemotherapy. Moreover, clinical symptoms and radiological features of PE usually cannot be distinguished from venous thromboembolism or embolism caused by tumor material.

Highest rates of VTE include the tumors of pancreas, ovary, kidney, lung, stomach, colon, rectum and brain [3]. The incidence is also high in patients with hematological malignancies such as leukemia, Hodgkin's disease, non-Hodgkin's Lymphoma and Myeloma ranging from 4.2% to 5% [4-7].

Diagnostics

The diagnosis of PE on the basis of only the clinical picture is difficult. Using pretest probability and clinical suspicion of this complication requires the initiation of anticoagulant therapy while simultaneous diagnostic work up is being done to achieve an accurate diagnosis. Testing may include serum D-dimer levels, blood gas analysis ECG, chest imaging study (X-rays, spiral CT, angio-CT, CT venography, magnetic resonance pulmonary angiography (MRPA), Ventilation Perfusion scan and CT angiography).

Determination of D-dimer is of limited clinical utility because of its low specificity (sensitivity 79 - 100%, specificity 25 - 100%). It is used to exclude the presence of thromboembolism (negative), as a positive result may only suggest the possibility of thrombosis. In addition, elevated levels of D-dimer are observed in several other cases which are associated with the formation or dissolution of fibrin, in patients with cancer, infections, heart and kidney failure, sepsis and leukocytosis, which make this marker as a single useful tool in the diagnosis of PE in patients with cancer [8,10].

Coagulation abnormalities

Coagulation abnormalities can be secondary to cancer. Most patients with cancer have blood coagulation test abnormalities indicative of up-regulation of the coagulation cascade system, increased platelet function abnormality like activation and aggregation, and increased proteolysis. The mechanisms responsible for this activation is very complex and can vary from release of cancer procoagulants, activa-

tion of host cells overactivity and expression of plasminogen activator inhibitor-1 and increased activity of proteins produced by the liver, including protein C, protein S and anti-thrombin (AT).

Chemotherapeutic agents may also contribute to hypercoagulability by tumor cells producing cytokines and procoagulants, producing toxic substances such as oxygen free radicals, that can damage and cause changes in the endothelium, and reduce levels of natural anticoagulants like proteins C and S and AT.

Chest radiography

Chest X-ray examination does not confirm or exclude PE. Approximately 50% of patients with PE will have chest x-ray abnormalities, such as enlargement of the pulmonary artery referred as Fleischner sign, cardiac enlargement (especially of the right ventricle), widened contour of the pulmonary trunk, and elevation of the diaphragm on the side of the embolism [12]. Sometimes Westermark sign suggesting oligemia can be seen secondary to PE. Patients with lung infarction sometimes have juxtapleural opacification (Hampton Hump). Parenchymal density, especially in patients with severe dyspnea or febrile patients, may be misinterpreted as atypical inflammatory changes. Radiological examination does not always allow the diagnosis of PE, but it enables us to exclude other diseases with similar clinical symptoms [10,11,15].

Chest tomography

CTPA is the imaging modality of choice for the diagnosis and work up of patients with suspected acute pulmonary embolism. CTPA has high sensitivity and specificity. PIOPED II trial demonstrating sensitivity of 83% and specificity of 96%. CTPA can rule out other etiology of chest pain and shortness of breath such as musculoskeletal injuries, vascular pathologies, pericardial abnormalities, pneumonia and sometimes even coronary artery disease [16]. However, there is a theoretical risk of cancer as a result of ionizing radiation. Advances in the techniques can minimize the amount of radiation [17]. Adverse events including anaphylactic reactions to iodinated contrast to low-osmolar and iso-osmolar contrast materials are low between 0.2% to 0.7% with fatal reactions occurring in 1 out of 170,000 injections [18-20].

Other imaging modalities

Lung scintigraphy (LS), uses radioisotopes for ventilation, perfusion, or both. It was the diagnostic study of choice in PE for about 30 years until better CT techniques developed [21]. Ventilation (V) and perfusion (Q) scans are not commonly used in the evaluation of PE diagnosis. It is used particularly in estimating the likelihood of its presence [22,23]. Although CTPA is the current gold standard, there are some scenarios VQ scan is preferred, particularly in patients with renal failure, contrast material allergies, young females and pregnant women, and patients who are extremely obese. VQ scan has up to 50-fold lower radiation dose to the breast [24,25], which makes sense to use in young females, including those who are pregnant. Perfusion scan can be performed before or after ventilation scan. If perfusion scan is performed first and normal, then the ventilation scan could be avoided, particularly in pregnant patients. Perfusion imaging alone is also considered in patients with suspicion of acute PE and sudden clinical deterioration as well as those who cannot remain still or hold his or her breath to do ventilation scan.

Doppler ultrasound of lower extremities is commonly used to detect the lower extremity venous thrombosis. CT venogram can be done at the same time as CTPA and will tell you more than what ultrasound can tell and increases the sensitivity for detection by adding to CTPA. There is additional radiation dose that will be added and in order to reduce radiation exposure, imaging of the iliac veins and inferior vena cava was not recommended and therefore not showing advantage over the ultrasound [26,27].

Magnetic resonance Pulmonary angiography (MRPA) has lower sensitivity of 78% especially in peripheral pulmonary arteries and high specificity of 99% on PIOPED III. Limitations noted, was mainly technically inadequate results. Therefore, should be considered only in highly experienced facility and where contraindications to standard testing exists [28].

Electrocardiogram

Electrocardiographic changes are not diagnostic but several changes can be seen. The most common ECG changes are tachycardia, supraventricular tachycardia. Some patients can present with atrial fibrillation or flutter. Non-specific changes in ST-T segment and negative T waves in leads V1-V3. Characteristic changes such as S1Q3T3 pattern or incomplete right bundle branch block can often occur during acute PE in 18%. Normal ECG can be seen in 17 - 20% of patients with massive PE [29].

Echocardiography

Echocardiogram has limited sensitivity and specificity of diagnosis of PE. Positive findings can be seen in cardiac and respiratory diseases without PE. It also helps in excluding other confounding diagnosis, patients that need emergent thrombolysis, monitoring response to therapy. Pulmonary embolism is associated with right ventricular overload. The changes include right ventricular enlargement and hypokinesis, enlargement of the pulmonary trunk, paradoxical septal motion, tricuspid insufficiency, widening of the inferior vena cava, decreased ejection fraction and thrombus in the right ventricle. Patients with these findings are at two fold increased risk of mortality whereas patients with normal echocardiogram has excellent outcome [15,30,31].

Treatment

Immediate treatment

Anticoagulation should be initiated as soon as the diagnosis of PE is suspected [34]. Unfractionated heparin may be preferred in patients who are candidates for further advanced therapies such as thrombolysis, catheter-directed thrombolytics or embolectomy, or surgical embolectomy because it can be adjusted and stopped for any required procedures [33]. Direct oral anticoagulants are first-line therapy for low-risk patients and intermediate- and high-risk patients once they have achieved hemodynamic stability [34,35].

Systemic thrombolytic therapy should be considered in massive PE to reduce mortality and recurrence [36]. Systemic thrombolytic therapy may be considered in high-risk submassive PE in the absence of any contraindications because it improves hemodynamics of the patient and prevent further decompensation, reverse RV dilatation, though no significant short-term mortality reduction has been noted [34,37]. Unfortunately, systemic thrombolytic therapy is associated with increased bleeding, including intracranial hemorrhage [37,38]. In patients who have relative contraindications to systemic thrombolytic therapy, reduced dose thrombolytic can be used because it still provides improvements pulmonary artery pressures and RV strain [39].

Catheter-directed therapy

Given the significant increased risks of systemic thrombolytic therapy like bleeding including intracranial bleeding, catheter-directed approaches have been used to reduce the dose of thrombolytics used or avoid systemic thrombolytics altogether. This modality of treatment has shown improvement in Right ventricular pressures and right ventricular thrombosis as these factors predict mortality and adverse effects like major bleeding, mortality, and recurrent PE [39].

Two catheter related approaches are currently used. One, catheter-directed thrombolytics wherein local delivery of lytic therapy to the pulmonary arteries. Second, catheter-directed mechanical thrombectomy, which may be used in isolation or in combination with lytic

therapy based on the critical nature of the patient and clinical scenario. Overall, the risk associated with catheter-directed therapies is low, with a 0.35% risk of ICH and 4.5% risk of major complications [40]. Therefore, current guidelines recommend use of catheter-directed lytics in intermediate-high-risk PE with relative contraindications to thrombolytic and use of catheter-directed thrombectomy in patients with absolute contraindications to thrombolytics or failed thrombolytic therapy [33].

Long term treatment

Historically, in patients with cancer, low molecular weight heparin (LMWH) has been the primary treatment choice for patients with VTE. Recently completed studies in patients with cancer-associated VTE have demonstrated efficacy of dabigatran, rivaroxaban, apixaban, and edoxaban as compared to warfarin. Bleeding rates with the direct oral anticoagulants (DOACs) has not been consistent.

Studies comparing DOACs to LMWH for treatment of cancer-associated VTE are ongoing and will provide further recommendations. But, DOAC therapy so far has not been inferior than LMWH. Use of DOAC therapy in cancer patients may be limited by potential drug-drug interactions like P-glycoprotein interactions and CYP3A4 interactions. Renal impairment and thrombocytopenia are both very common in patients with active cancer and may impact the safety of DOAC therapy. Using a DOAC with less renal clearance should be cautious and some are preferable to others. Avoiding anticoagulation when platelet counts are < 50,000 is often recommended. DOAC therapy is associated with lower intracranial hemorrhage risk than warfarin. Most patients with cancer-associated thrombosis will require treatment as long as the cancer is active (until remission or resection). Extended treatment may be considered based on overall risk: benefit assessment based on stage of the disease and other risk factors. Hospitalized patients with active cancer are at high risk for thrombosis and should receive aggressive thromboprophylaxis as long as there is no significant high risk of bleeding [32].

Prognosis

In patients with the diagnosis and appropriate standard treatment of PE the mortality rate is 2 - 8%. Mortality rises to about 30% in patients not treated, mainly due to the lack of correct diagnosis. Some patients with Massive PE with hemodynamic compromise mortality increases to 30 - 35%. In contrast, in patients without hypotension prognosis is determined on the basis of echocardiography, and the absence of right ventricular overload is a positive prognostic factor. The choice of treatment in the acute phase of the disease depends on the assessment of prognosis, defined on the basis of clinical status. In patients without symptoms of shock and without significant systemic hypotension biochemical indices of heart damage and cardiac overload should be measured as a basis for prognosis [42].

Factors that increase the risk of death in the acute scenario include right ventricular failure (HR 2.4, 95% CI 1.5 - 3.7), right ventricular thrombosis, hemorrhagic complications following thrombolytic therapy or anticoagulation, subsequent embolic episode, and comorbidities, especially cancer (HR 2.3, 95% CI 1.5 - 3.5) [41].

The risk of recurrent PE is highest within 6 weeks after the first thromboembolic episode, but effective treatment reduces it to 8% [41].

Discussion

Cancer itself is an individual risk factor for PE. Oncological treatment such as surgery, radiotherapy, chemotherapy and hormone therapy increases the risk of thrombosis and embolism, among other things due to the release of procoagulants and cytokines from cancer cells as well as the toxic effect acting on the vascular endothelium, and the reduction in the concentration of protein C, protein S and Antithrombin III.

Intensive chemotherapeutic regimens increase thrombotic microangiopathy after high-dose chemotherapy combined with autologous or allogeneic transplantation of hematopoietic cells. The estimated incidence of this is 2 to 8% of patients treated with systemic therapy.

This can appear between 2 - 9 months after the completion of chemotherapy even when the cancer itself is in remission. Several chemotherapy drugs also increase the risk of microangiopathy picture. Radiotherapy alone increases the predisposition to the occurrence of thromboembolic disease, and chemotherapy combined with radiation of the whole body has an additive effect [1,43]. The prognosis or outcome of this complication is poor and mortality is as high as 31%. It is thought that the mechanism of the pathogenesis is chemotherapy-induced damage to the vascular endothelium.

There is no universal practice of prophylactic anticoagulation although there was some data suggesting low dose warfarin decreased incidence of VTE than no anticoagulation patients but was not statistically significant. It is well known that thromboembolic disease in patients with cancer occurs in advanced disease and is associated with poor prognosis. Studies indicate that the incidence of acquired resistance to activated protein C is higher in cancer patients than in patients without cancer. Patients with inherited thrombophilia or acquired thrombophilia affecting the coagulation system due to cancer are at increased risk of pulmonary embolism compared to patients who do not develop these acquired thrombophilia factors. The literature mentions a number of other conditions that may significantly influence the processes of coagulation in patients with cancer, but the exact mechanism is not completely understood.

Venous thromboembolism is common in patients with any cancer and the incidence is increased by surgery, chemotherapy, radiotherapy and disease progression. In many studies the authors found that pre-treatment abnormalities of coagulation in patients with cancers were significantly correlated with survival. Low molecular weight heparin has been used for over 20 years in the prophylaxis of VTE and has been shown to be the drug of choice in the treatment of VTE in cancer patients. Recent data is also showing DOAC are also effective in long term treatment in cancer patients. However, there is very limited data for primary thromboprophylaxis in cancer patients routinely unless there are associated risk factors requiring prophylaxis.

Summary

Oncology patients are at high risk for thromboembolism. There is increased risk of developing thromboembolic episodes before, during and after the diagnosis of cancer. The deterioration of the patient in these cases is sometimes interpreted as a failure of therapy, complication after oncological treatment or progression of cancer which also can mimic the same symptoms making it difficult to establish the correct diagnosis or delay in diagnosis resulting in the lack of timely implementation of appropriate treatment.

The priority of treatment for cancer might sometimes result in overlooking the symptoms of pulmonary embolism. Therefore, primary care physicians, hospitalists, and medical oncologists must have a low threshold for diagnosis because fast timing to initiate treatment with anticoagulation prevents adverse events and decreases mortality.

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