CLINICAL VIGNETTE

How to Approach Low Risk Pulmonary Embolism: A Case Report and Discussion

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Introduction

Venous thromboembolism (VTE) is a common and significant problem with a wide variance of potential clinical presentations. In the United States, approximately 1% of all hospital admissions are for VTE. It is estimated there are 900,000 cases yearly resulting in 60,000 to 300,000 deaths.[1] Patients can present with symptoms acutely (immediate), subacutely (within days to weeks), or chronically (years). Clinical presentation of pulmonary embolic events, in particular, can range from minimal to no symptoms, to catastrophic right-sided heart failure, and death.

In cases of pulmonary embolism, it is generally agreed that patients having hemodynamic instability, risk for significant clinical deterioration, requirement for oxygen supplementation, uncontrolled symptoms, and any other possible complication require initial admission for management, which may include subspecialty consultation, invasive measures, and intensive care depending upon the clinical context. However, it is sometimes more difficult to decide what is required for uncomplicated cases with low suspicion for morbidity and mortality. We present such a case of low-risk pulmonary embolism and discuss the evidence-based approach to management of such situations.

Case Report

A 65-year-old man with a past medical history of benign prostatic hyperplasia presented with a one-week history of chest pain. The pain was classified as sharp in quality, initially localized to the left side of the chest, but migrated to the right side over the course of the week. The pain was worse with deep inspiration. There was no exertional component to the chest pain. He denied any frank shortness of breath, palpitations, lightheadedness, cough, or wheezing.

The patient denied any recent surgeries or significant trauma but had taken a 10-hour automobile journey two weeks prior to the initial onset of symptoms, which was only interrupted by a few brief rest stops with minimal ambulation. He had no prior history of thromboembolic events and had no family history of hypercoagulability.

Given the ongoing chest pain over the one-week period without improvement, the patient presented to the emergency room for further evaluation. On arrival, he was afebrile and otherwise hemodynamically stable (blood pressure 140/70 mmHg and pulse 75 beats per minute), with oxygen saturation 97% on room air. Initial laboratory studies were notable only for an elevated D-dimer at 2310. Complete blood count and comprehensive metabolic panel were unremarkable. Bilateral lower extremity Doppler ultrasound showed no evidence of deep venous thrombosis. Chest CT angiography revealed segmental pulmonary emboli in the right upper and lower lobes, as well as the left lower lobe, with wedge-shaped infarction distal to these emboli. There was no evidence of right heart strain suggested by chest CT or electrocardiogram.

The patient was considered to be low risk for development of further complications. His pain was generally mild, not requiring narcotics for control. He did not require oxygen supplementation to maintain adequate oxygen saturation. His blood pressure and heart rate were within normal limits. The emergency room physician discussed the case with his primary care provider, who requested that the patient be admitted to the hospital for initiation of anticoagulation with workup for potential hypercoagulability.

The patient was admitted overnight to the hospital. He was initiated on enoxaparin, which was transitioned to rivaroxaban the following day. A hypercoagulable laboratory investigation was sent, including Factor V Leiden mutation, protein C and S activity, serum and urine protein electrophoresis with immunofixation, beta-2-glycoprotein, and anti-cardiolipin antibody. The patient's chest pain continued to remain well-controlled without the use of narcotics. His hemodynamics and oxygen saturation remained stable. Ultimately, the hospitalist team felt he most likely had a provoked thromboembolic event related to his recent extended automobile trip. Given stability, he was discharged home on rivaroxaban on hospital day 2 with hypercoagulability tests pending as described above.

The patient followed up with his primary care provider the following week. His symptoms had resolved. Somewhat unexpectedly, his kappa light chain levels were mildly elevated, and immunofixation was consistent with monoclonal gammopathy. Other hypercoagulability tests were unremarkable. The patient was referred to hematology. CT of the abdomen and pelvis was performed and was unremarkable. The hematologist sent additional hypercoaguable tests, including prothrombin 2010A variant, carcinoembryonic antigen (CEA), CA 19-9, and PSA levels, all of which resulted normal. His hematologist felt that he indeed most likely had a provoked spontaneous thromboembolic event. The mild elevation in kappa light chain was felt to be most consistent

with monoclonal gammopathy of undetermined significance (MGUS); this was felt to be unrelated to the presenting issue. The patient was anticoagulated for a total of 9 total months without recurrent symptoms or complications. His kappa light chain levels have been followed serially and remain stable.

Discussion

The first therapeutic intervention for stable patients with pulmonary embolism (PE) is systemic anticoagulation, which should be started immediately. There are several options for initial care. Most patients will be initiated on low molecular weight heparin (given subcutaneously once or twice daily), fondaparinux (given subcutaneously once daily), or unfractionated heparin (via continuous intravenous infusion). However, novel oral anticoagulants rivaroxaban and apixaban (both factor Xa inhibitors) have also been FDA-approved for initial monotherapy for PE, and they do not require bridging with a heparin product. All other oral anticoagulants, including warfarin, dabigatran (a direct thrombin inhibitor), and edoxaban (another factor Xa inhibitor) require a short-course of bridging with a heparin product. Interestingly, dabigatran and edoxaban may ultimately become approved for initial monotherapy with greater experimental evidence, but the current recommendation is to bridge them with a heparin product. 2012 Chest guidelines prefer low molecular weight heparin and fondaparinux over unfractionated heparin, and do not specifically address the immediate use of oral rivaroxaban or apixaban.[2]

After initial diagnosis and stabilization of a patient with pulmonary embolism, the next step in management is assessment of risk for further complication. There are two widely-known models for estimating risk: the Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI).[3,4] The PESI assigns a risk score based upon: age; gender (higher risk for male patients); history of cancer, heart failure, or chronic lung disease; pulse >110 beats per minute; systolic blood pressure <100 mmHg; respiratory rate >30 breaths per minute; temperature less than 36^{o} C; altered mental status; and oxygen saturation <90%. With PESI, low-risk patients are estimated to have <2% risk for inpatient death or non-fatal complication.[3] The sPESI evaluates for the presence of age >80, history of cancer, chronic cardiopulmonary disease, pulse >110 beats per minute, systolic blood pressure <100 mmHg, and oxygen saturation <90%. Low risk patients have none of these (score of 0), and low risk sPESI with normal serum troponin and brain natriuretic peptide (BNP) has a negative predictive value of 99-100% for death, hemodynamic collapse, or recurrent pulmonary embolism within 30 days.[4]

For low-risk patients, there is limited experimental evidence directly comparing outpatient with inpatient management. 2012 Chest guidelines somewhat vaguely advocate for "earlier discharge" (compared with discharge after 5 hospital days) in those patients with "low-risk PE and whose home circumstances are adequate."[2] These recommendations include the possibility of immediate discharge (without any admission) as a feasible option, but do not specifically address outpatient management independently. Meanwhile, a Cochrane review from 2014 found insufficient evidence to adequately assess safety and efficacy of inpatient versus outpatient treatment for low risk acute PE.[5] Nevertheless, this remains an area of active investigation. It has been proposed that outpatient anticoagulation is safe and effective in those patients with all of the following: low-risk PESI or sPESI score, no requirement for supplemental oxygen, no requirement for narcotics for pain control, no respiratory distress, normal pulse and blood pressure, no recent history of bleeding or risk factors for bleeding, no serious comorbid medical conditions (ischemic heart disease, chronic lung disease, renal or liver failure, thrombocytopenia, or cancer), normal mental status, good home support, and absence of concomitant lower extremity deep venous thrombosis.[6]

Another common clinical question is whether a patient presenting with PE should be evaluated for potential hypercoagulability, and if so, what tests should be sent. It is generally agreed that the Virchow's triad, which includes venous stasis/immobility, trauma (vascular endothelial injury), and hypercoagulability (inherited or acquired) represents the underlying pathogenesis of venous thromboembolism. Common predisposing conditions include long travel (immobility), surgery (trauma), physical injury (trauma), co-morbid illness (such as cancer, with acquired hypercoagulability), and medication-related (such as hormone replacement, with acquired hypercoagulability). A thorough history and physical examination will commonly suggest an underlying pathogenesis. Beyond this initial assessment, it has been suggested that all patients undergo the following routine tests: complete blood count with smear, routine coagulation studies, erythrocyte sedimentation rate (which, if elevated, could suggest underlying malignancy or connective tissue disorder), fecal occult blood testing (which could suggest gastrointestinal malignancy), serum chemistries with liver and renal testing, and no imaging beyond that required to make the diagnosis of VTE.[7] Further testing can be performed as indicated by abnormalities in this initial workup.

In the absence of abnormality found in this initial laboratory workup, further advanced testing for hypercoagulability in such patients with an initial episode of VTE is not indicated.[8] However, further testing is potentially indicated in certain subsets of patients, including younger patients (under 45), those with family history of VTE in first degree relative before age 45, patients with recurrent VTE, thrombosis in multiple or atypical sites (such as portal, mesenteric, or cerebral veins), or those with arterial thrombosis.[9] The proposed initial serologic workup for hypercoagulability (if it is being sent) includes: factor V Leiden mutation (or activated protein C resistance assay), prothrombin 201210A gene mutation test, protein C and S activity levels, and antithrombin activity. If routine coagulation studies are abnormal (most notably if aPTT is prolonged without explanation), tests for antiphospholipid antibody syndrome can also be sent, which include anticardiolipin antibody, beta-2-glycoprotein antibody, and the lupus anticoagulant.[7,8] With regards to occult malignancy as a precipitant of acquired hypercoagulability, only routine, age-appropriate cancer screening is felt to be indicated for initial VTE in patients without abnormalities suggested on routine initial tests. Should the patient develop recurrent episodes/episodes while on therapeutic anticoagulation, suggested additional screening tests could include computed tomography of the chest, abdomen, pelvis, and tumor markers (CEA, alpha-fetoprotein, CA 19-9, CA 125, and PSA).[7]

Positron emission tomography, or PET/CT, is not a validated screening tool for malignancy, and randomized trials have failed to show benefit from its use in screening.[10]

Conclusion

Our 65-year-old patient with no co-morbidities had a PESI score of 75 (age and male sex) and sPESI score of 0, quantifying him as low-risk for morbidity and mortality. It could be argued that he could have been managed as an outpatient, but certainly the brief nature of his hospitalization was warranted. Rivaroxaban was a reasonable choice for initial anticoagulation, and if immediately available, it could have been given without any need for enoxaparin.

Given his age, lack of co-morbidities, and apparent provocation of the VTE event, workup for hypercoagulability was not warranted. The workup, however, did reveal an unrelated issue (MGUS) that led to further expansive medical testing (CT of abdomen and pelvis, as well as repeated rechecks of light chain levels), and ultimately have not impacted outcome in any way. (at least to this point).

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