CME Article

How I treat incidental pulmonary embolism

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The identification of pulmonary embolism (PE) on computed tomography scans performed for indications other than identification of thromboembolism is a growing clinical problem that has not been adequately addressed by prospective treatment trials. The prevalence of incidentally detected PE ranges from 1% to 4% in unselected populations, with higher rates among hospital inpatients and patients with cancer. Current guidelines recommend using the same approach to type and duration of anticoagulation as is used for patients with suspected PE. Available data regarding the significance of symptomatic subsegmental PE (SSPE) are conflicting, making it difficult to draw conclusions about the appropriate treatment of incidentally detected SSPE, for which the data are sparse. Among cancer patients, the bulk of available data suggest that incidental SSPE is associated with recurrent venous thromboembolism and, when symptomatic, may adversely impact survival. Here, the topic is reviewed utilizing 3 clinical cases, each of which is followed by a discussion of salient features and then by treatment recommendations. (*Blood*. 2015;125(12):1877-1882)

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Learning objectives

1. Describe the influence of clinical characteristics and imaging modalities on the detection of incidental pulmonary embolism.
2. Discuss recommendations for the management of incidental pulmonary embolism in patients with cancer.
3. Discuss recommendations for the management of subsegmental incidental pulmonary embolism.

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Case A

A 55-year-old man was referred for a computed tomography (CT) scan of the chest after a preoperative workup revealed an abnormal chest radiograph. The patient was being considered for gastric bypass surgery to reduce obesity-related complications including diabetes and hypertension. A 16-slice multirow detector CT scan of the chest using intravenous contrast revealed right lower lobe atelectasis as well as a calcified right hilar lymph node measuring 0.9 cm, which was thought to be consistent with old granulomatous disease. However, a left lower lobe segmental pulmonary artery filling defect was also identified. The ordering physician was contacted and immediately evaluated the patient in clinic. The patient denied cough, chest pain, shortness of breath, or leg swelling. Vital signs demonstrated slightly elevated blood pressure of 147/89, normal heart rate of 82, and an oxygenation saturation of 97% on room air by pulse oximetry. Physical examination revealed normal breath sounds and normal heart rate and rhythm without a right ventricular heave or prominent second heart sound.

Silent, unsuspected, or incidental?

The patient in this clinical scenario has been diagnosed with an incidental pulmonary embolism (IPE). This term is applied to the presence of 1 or more pulmonary artery filling defects identified on a CT

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scan performed for indications other than evaluation of PE. This finding has also been referred to as "silent PE," and my group has used the term "unsuspected PE" in published reports because retrospective data suggest that many affected patients had actually reported symptoms suggestive of PE.[1] However, in the interest of uniformity I now advocate using the term "incidental" PE, or IPE, as recommended by the International Society on Thrombosis and Haemostasis.[2] PE location is classified based on the most proximal pulmonary arterial segment involved: main, lobar, segmental, or subsegmental.

Impact of radiologic technique on identification of IPE

The advent of multislice multidetector-row CT (MDCT) scanning in 1998 signaled a breakthrough in CT technology by significantly increasing the speed of scanning. Faster scan speed results in a larger potential imaging volume during a single breath hold, a lower required dose of contrast, and a shorter breath-hold time for the patient.[3,4] In contrast to the single-detector-row CT (SDCT) scanners, faster scan speed does not compromise spatial resolution. In fact, the potential size of the individual images or slice thickness has decreased from 3 to 5 mm with SDCT to 2.5 mm with 4-slice MDCT to as thin as 0.625 mm with 16-slice MDCT.[4,5] Thinner slices are associated with better visualization of the more distal segmental and subsegmental pulmonary vasculature,[5] even when the scan is not specifically optimized for viewing the pulmonary arteries. Thus, thinner slices are also associated with a greater incidence of IPE.[5] Isolated subsegmental pulmonary embolism (SSPE), in particular, is more likely to be identified on 16-slice scanners than on 4-slice or SDCT scanners.[6] The frequency of identification of IPE may increase with the level of experience of the radiologist, and interobserver agreement between radiologists is lower with more distal filling defects.[7]

CT pulmonary angiography (CTPA), which is performed to optimally visualize the pulmonary arterial tree, is also now routinely done using multirow detector scans and will therefore be referred to in this article as MD-CTPA. MD-CTPA is particularly reliant on the timing of the contrast injection to optimally enhance the vascular bed of interest. Because of the rapidity of MDCT image acquisition, the contrast bolus can be completely missed resulting in inadequate opacification of the pulmonary arteries and an indeterminate scan.[6] This highlights an important difference between a routine MDCT scan of the chest and MD-CTPA, which is that the standard contrast injection flow rate for a routine scan is usually ~4 mL/s. A higher rate of injection may be more optimal for pulmonary artery opacification; alternatively, a higher iodine concentration can be employed, or the delay from injection to scan time can be increased. Heart failure and pulmonary hypertension can result in poor circulation of contrast. Thus, most MD-CTPA protocols use a test bolus to determine the amount of time the contrast will take to opacify the target arterial bed.[6] Obesity can result in more noise or artifact and may require acquisition of thicker slices, which can in turn reduce sensitivity for small clots. Based on these factors, one would expect a higher false-negative rate of PE detection on MDCT as compared with MD-CTPA among obese patients. However, respiratory artifact, often attributable to severe dyspnea, can result in false-positive results because of volume averaging of an artery with surrounding lung.[8] Therefore, in this obese patient without dyspnea, the identification of IPE in the segmental artery is unlikely to be a false-positive finding, so additional testing with MD-CTPA would expose the patient to more radiation and more contrast and would not likely change the management.

Many centers routinely scan the proximal lower extremities for deep venous thrombosis (DVT) as part of the MD-CTPA protocol. Therefore, in this case, where no lower extremity venous imaging is available, one might consider Doppler ultrasonography of the lower extremities to ascertain the degree of clot burden in the patient and enhance the confidence with which to recommend anticoagulation. This strategy has not proved to have high yield among a large series of patients undergoing evaluation for suspected PE without symptoms or risk factors for DVT, in whom only 1.7% had an abnormal finding on lower extremity ultrasonography.[9] On the other hand, a majority of patients with PE have concomitant DVT at autopsy, and these low rates of detection may reflect lower sensitivity of ultrasonography.[10] Furthermore, the presence of concomitant DVT is associated with higher all-cause and PE-related mortality at 3 months among patients presenting with symptomatic PE.[11] Although the use of lower extremity ultrasound has not been systematically evaluated among patients with IPE, I recommend it when I am asked to evaluate such patients at the time of IPE diagnosis.

Case A treatment recommendations. This patient actually has none of the risk factors associated with IPE. A meta-analysis of studies published through 2009 indicated that the highest weighted mean prevalence of IPE occurs in inpatients (4.0%) and cancer patients (3.1%), with older age and prior venous thromboembolism (VTE) also increasing the risk.[12] Moreover, by review of symptoms and physical exam the patient is truly asymptomatic, and a lack of PE-related symptoms has been associated with low early mortality rates after IPE in patients with and without cancer.[13,14] Nevertheless, the 2012 American College of Chest Physicians guidelines recommend using the same pharmacologic treatment strategy for IPE as is currently recommended for suspected PE.[15] This is a consensus-based recommendation, as there are few studies that examine the natural history of patients with IPE not treated with anticoagulation. In the standard-setting trial by Barritt and Jordan, 19 patients with acute symptomatic PE were left untreated, whereas 16 symptomatic patients were given intravenous heparin.[16] Almost 25% of the untreated patients died, and an additional 5 untreated patients had progression of PE at 3 months, whereas none of the patients treated with anticoagulation suffered PE-related death or progression. Further randomization was halted as this was considered an unacceptable fatality rate and, since that publication, the inclusion of an untreated control group of patients with symptomatic PE would be considered unethical. Nonetheless, the study also demonstrated that ~50% of patients with symptomatic PE who were left untreated survived without short-term (3 month) progression.

The outcome of patients with asymptomatic IPE who are left untreated may be much better than in symptomatic, suspected PE. In a study of patients undergoing total hip and total knee replacements, 64-row MD-CTPA was performed between 24 and 36 hours postoperatively but not read until the completion of clinical trial enrollment.[17] All patients received prophylactic-dose low-molecular-weight heparin (LMWH) beginning postoperative day 1 and continuing for 10 days after hip replacement and 21 days after knee replacement. Eleven of 27 (41%) of the knee replacement patients and only 1 of the 21 hip replacement patients had IPE, none of which were isolated subsegmental clots. At 3-month follow-up, no patient with IPE died or developed PE-related symptoms. Short-term outcome appears to have been very good among these postarthroplasty patients with IPE who did not receive the recommended treatment dose or duration of anticoagulation therapy for PE; however, the potential treatment impact of the prophylactic-dose LMWH used in this study cannot be discounted.

Only 1 trial has addressed the role of withholding anticoagulation for patients with asymptomatic PE in a randomized fashion.[14]

Patients with venographically confirmed DVT but without PE-related symptoms were evaluated with a perfusion-ventilation lung scintigraphy and randomized to receive intravenous heparin followed by oral anticoagulation (n = 57) or a nonsteroidal agent (phenylbutazone) for 10 days without anticoagulation (n = 57). The majority of the patient population (45%) had either no risk factors or an orthopedic risk factor, and a small percentage (12%) had malignancy. Among the patients whose DVT was distal to the popliteal vein, 33% had PE, whereas 53% of those with more proximal DVT had PE. In total, 46 patients with asymptomatic PE were treated with anticoagulation, and 41 were observed. At 10 days and 60 days, there was no significant difference in the rate of progression, regression, or stable findings on perfusion-ventilation scanning, and the only recorded death occurred in the anticoagulated group. These data are unlikely to be replicated given the plethora of published trials supporting the use of anticoagulation in the short and long term for patients with symptomatic DVT, and it is possible that ventilation-perfusion mismatch is not a relevant measure of anticoagulation efficacy in the short term. Nonetheless, it does highlight the potential for endogenous fibrinolysis to resolve acute PE among patients not given anticoagulation; this effect may be more potent in patients who are truly asymptomatic.

Notwithstanding the possibility that small or asymptomatic PE may resolve without anticoagulation in certain patient populations, based on the current guidelines and the lack of adequately powered studies to justify withholding anticoagulation, I would treat the patient in case A with full-dose anticoagulation, starting with outpatient LMWH and transitioning to warfarin, for at least 3 months. I would postpone the elective surgery until completion of treatment and would transition back to LMWH, which has a predictable half-life, for several days prior to surgery. The last preoperative dose should be given 24 to 36 hours prior to surgery. It is also reasonable to consider one of the direct oral anticoagulants (DOACs) for this patient. Dabigatran, rivaroxaban, and apixaban are approved in the United States for the treatment of VTE.

The duration of anticoagulation that should be recommended for this patient is not clear from available studies. The IPE in this case is considered idiopathic because there is no identifiable reversible risk factor. The literature suggests that recurrence rates are as high as 30% at 5 years after completion of anticoagulation in patients with idiopathic VTE.[15] However, it is not clear if the recurrence rates are this high after an idiopathic IPE. A careful evaluation of the risks and indications of indefinite anticoagulation must be conducted with the patient in this case. If he is amenable, I would transition from postoperative prophylaxis back to full-dose oral anticoagulation once the postoperative bleeding risk is considered minimal. Either warfarin or apixaban, which has excellent efficacy and safety data for long-term prevention of recurrent of VTE,[18] would be appropriate unless the patient develops new risk factors for bleeding or a strong preference to avoid long-term anticoagulation.

Case B

A 52-year-old woman with a history of stage III colorectal cancer resected 2 years prior presented for routine follow-up. She reported fatigue to the nurse without other symptoms. The oncologist's evaluation revealed normal vital signs and a normal physical examination. A contrast-enhanced CT scan of the chest, abdomen, and pelvis was performed for routine staging and demonstrated a new 1.6-cm liver mass suspicious for malignancy. However, a large left main pulmonary artery filling defect along with 2 additional left lower lobe segmental PEs were also identified.

This patient, whose scan suggests a likely recurrence of colorectal cancer has developed IPE involving the main pulmonary artery despite normal physical examination and vital signs. It is not uncommon to identify large and/or proximal PE incidentally in cancer patients, despite a lack of physical examination signs. A meta-analysis of studies published through 2009 found that ~50% of IPE occur in the main or lobar pulmonary arteries.[12]

Can IPE impact cancer survival?

Studies reporting on the survival impact of IPE in cancer patients have used as the comparator arm either cancer patients with symptomatic PE or cancer patients with no evidence of PE. Dentali and colleagues found no difference in 6-month mortality between 60 cancer patients with IPE (47.5%) and 120 cancer patients diagnosed with PE based on suggestive symptoms (45.0%).[19] Both groups fared significantly worse than the 60 symptomatic cancer patients in whom PE was ruled out (6-month mortality 26.7%). These results are in accordance with those of den Exter et al, who reported 12-month mortality of 52.9% among cancer patients with IPE and of 52.8% among cancer patients with symptomatic PE.[20] They also found no difference in major bleeding (12.5% and 8.6%) or in recurrence (9.8% and 10.4%) between the IPE and the symptomatic PE groups. Our group found a hazard ratio for death at 6 months of 2.28 for cancer patients with IPE more proximal than the subsegmental arteries as compared with well-matched cancer patients without PE.[21]

Although this patient's PE was unsuspected by the treating physician who ordered her scan, she did report fatigue to the nurse. In our descriptive analysis of 46 cancer patients with IPE, 54% complained of fatigue to someone on the medical team as compared with only 20% of age- and stage-matched control patients with the same cancer who did not have VTE.[1] We suspect that oncologists may misattribute patients' reports of fatigue to cytopenias, chemotherapy treatment, and/or the underlying malignancy. By using a well-matched control group, our study suggests that patients' reports of fatigue may actually reflect dyspnea on exertion or other PE-related cardiopulmonary symptoms. In fact, in a follow-up study that included 24 additional cancer patients diagnosed with IPE, we found that the presence of fatigue or shortness of breath conferred significantly poorer survival as compared with those who were truly asymptomatic at the time of their IPE.[13]

Case B treatment recommendations. Given the identification of proximal IPE, the likely underlying malignancy, and the lack of a contraindication to anticoagulation in this patient, I would initiate anticoagulation with treatment-dose LMWH. This is in accordance with American College of Chest Physicians and American Society of Clinical Oncology consensus recommendations.[15,22] There is only 1 published study that included a significant number of cancer patients with IPE who were left untreated.[23] In this study of 113 lung cancer patients with IPE, the 62 patients who were not treated with anticoagulation had significantly poorer median survival (6.1 months) as compared with the treated patients (30.9 months).

The recommended duration of anticoagulation for patients with cancer-related VTE is 3 to 6 months with ongoing therapy if the malignancy persists. LMWH is still the treatment of choice in this group as there is less bleeding and less recurrence than with oral vitamin K antagonists.[15,22] A recent meta-analysis that addressed the outcomes of cancer patients enrolled in VTE treatment trials comparing various DOACs to standard heparin followed by vitamin K

antagonists demonstrated a nonsignificant reduction in recurrent VTE and major and clinically relevant nonmajor bleeding.[24] The authors concede that event rates were lower in both groups than in previous trials, suggesting that the cancer patients included in these treatment trials may not have been as challenging as the typical cancer patient with VTE.

After the initial treatment course of LMWH, patients may desire an alternative agent because of prohibitive cost or discomfort from injections. In this case, I do offer them the opportunity to switch to warfarin, although I admonish that variability in anticoagulant effect will be a major ongoing issue and is affected by their diet, concomitant medications, and chemotherapy effects. I discuss the DOACs as well, but I emphasize the potential for interactions with chemotherapy drugs, the inability to assess resultant drug levels, and the lack of reversal agents. Without safety data regarding their use in conjunction with chemotherapy and the bleeding risks specific to patients with cancer, I do not currently recommend the DOACs to cancer patients outside of clinical trials.

Case C

A 70-year-old man was recently discharged from the hospital where he underwent laparoscopic nephrectomy for renal cell carcinoma. He completed only 1 week of prophylactic LMWH therapy in the postoperative period because he developed melena requiring transfusion of 2 units of packed red cells. Endoscopy revealed an ulcer in the gastric antrum without active bleeding. He was discharged ambulating and with normal renal function on postoperative day 12 and returned to the oncology clinic 2 weeks later for evaluation. He stated he felt well, was independently pursuing all activities of daily living, and was having normal daily bowel movements without melena. His vital signs were within normal range, and physical examination demonstrated normal respiration and a normal S1 and S2 with the exception of a 2/6 systolic ejection murmur that was present prior to the surgery. His laparoscopic wounds were healing as expected. A staging CT scan of the chest, abdomen, and pelvis with intravenous contrast revealed bilateral pulmonary nodules, slightly reduced in size and number from the prior scan. Also noted was a left lower lobe subsegmental pulmonary artery filling defect.

This patient with presumed metastatic renal cell carcinoma has an incidental SSPE (ISSPE), or the unexpected finding of 1 or more filling defects occurring no more proximally than the subsegmental branches of the pulmonary arteries. He is asymptomatic and has had a recent surgery and prolonged hospitalization because of a bleeding episode that occurred while he was being treated with prophylactic doses of LMWH.

What do we know about subsegmental PE?

The preponderance of data regarding SSPE come from studies performed with patients evaluated for symptoms suggestive of VTE, rather than from patients with incidentally detected SSPE. In a meta-analysis of studies evaluating patients suspected to have PE, the rate of isolated SSPE was 9.4% in patients that underwent MD-CTPA compared with 4.7% in patients that underwent a single-detector CTPA.[25] Despite the increased prevalence of SSPE on MD-CTPA, the 3-month risk of recurrent VTE was no worse in the group evaluated with single-detector CTPA and left untreated with a negative study. So the authors suggest that SSPE may not be clinically relevant, even among patients with symptoms suggestive of PE.[25] Indeed, in a retrospective analysis of 93 symptomatic patients found to have isolated SSPE, 22 were left untreated and 71 received anticoagulation.[26] A majority (20/22) of the untreated patients had negative duplex ultrasonography of the lower extremities. At 3-month follow-up, there were no major bleeds, recurrence, or deaths in the untreated group; whereas among treated patients, there were 5 major bleeds, 3 minor bleeds, 2 deaths unrelated to PE, and 1 recurrent VTE. Given the retrospective nature of the study, it is certainly possible that clinicians chose to treat higher-risk patients such as patients with malignancy or other comorbid conditions potentially accounting for the poorer outcomes seen in the treated group. However, at least with respect to recurrent VTE, there was no significant increase among patients with SSPE and without DVT who were left untreated.

Are cancer patients with SSPE different?

In contrast to the earlier findings, den Exter and colleagues performed a meta-analysis in which they compared 116 symptomatic patients diagnosed with SSPE to 632 symptomatic patients with more proximal PE and found no difference in VTE recurrence, major bleeding complications, or mortality at 3 months.[27] Notably, the presence of malignancy was a significant independent contributor to recurrent VTE in both groups. In our retrospective series of cancer patients with IPE, the 17 with ISSPE had similar survival to their age- and stage-matched controls, whereas those with more proximal PE had significantly poorer survival than controls.[21] However, most were treated with anticoagulation. Subsequent analysis of the cohort demonstrated that the presence of PE-related symptoms, especially fatigue and shortness of breath, adversely impacted survival.[13] Individual studies of cancer patients with IPE generally include very few with ISSPE, but a recent meta-analysis of cancer patients with IPE included 193 patients with ISSPE whose outcome with respect to recurrent VTE did not differ from patients with more proximal IPE.[28] Unfortunately, data regarding symptoms were not available for all of these patients, and so the impact on survival could not be assessed. In summary, although there appears to be some discrepancy in the published outcomes of unselected symptomatic patients diagnosed with SSPE, the diagnosis of ISSPE in patients with malignancy is associated with recurrent VTE and therefore merits anticoagulation in the absence of a contraindication. Moreover, the presence of symptoms among cancer patients with ISSPE may correlate with poorer survival.

Case C treatment recommendations. A recent Cochrane systematic review found insufficient data to recommend for or against anticoagulation for patients with symptomatic SSPE or ISSPE.[29] Treatment guidelines for PE have not been based on the location, size, or number of filling defects.[15] Additional diagnostic evaluations that might be used in patients with suspected PE include lower extremity duplex ultrasonography and plasma d-dimer testing. However, as mentioned previously, lower extremity duplex ultrasonography may have low yield in patients without symptoms, and d-dimer has been shown to be less sensitive for SSPE[30]; nevertheless, these studies were performed in patients suspected of having PE. Because of the adverse survival impact of VTE in cancer patients,[31] and in order to get a better sense of overall clot burden, I would pursue lower extremity duplex ultrasonography to evaluate for the presence of DVT in the patient in case C. There are no data evaluating plasma d-dimer levels in cancer patients with SSPE, and the recent bleed, surgery, and ongoing active malignancy all may affect the results, so d-dimer testing could not be used to guide management in this case. If the ultrasound is negative for DVT, given the patient's lack of

PE-related signs or symptoms and his recent major bleeding event, it is reasonable to consider withholding anticoagulation with close follow-up, such as repeat lower extremity venous ultrasonography or even MD-CTPA in 1 to 2 weeks. On the other hand, he presumably has ongoing active malignancy (lung metastases) and is therefore more likely to suffer recurrent VTE. On that basis, it is entirely reasonable to treat with full-dose LMWH. The patient is more than 2 weeks out from his acute gastrointestinal bleed and shows no evidence of ongoing bleeding, so anticoagulation is not contraindicated.[32] I would not favor placement of an inferior vena cava filter in this case, especially without evidence of a concomitant DVT. This recommendation is in keeping with the 2013 ASH Choosing Wisely campaign, which reviews the current literature on the use of inferior vena cava filters.[33]

Conclusions

The identification of IPE can be a challenging clinical problem. Current management strategies do not differ from those proposed for symptomatic PE, and the preponderance of data suggest that these events are clinically significant. Data are conflicting as to whether it may be safe to withhold anticoagulation for patients with ISSPE. However, at least among patients with cancer, these events do appear to be associated with VTE recurrence and, when symptomatic, may adversely impact survival. Clinical trials should specify when VTE are identified incidentally and should also record related symptoms, including fatigue, the presence of concomitant DVT, and VTE-related outcomes, including recurrence, bleeding, and mortality.

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