Grand Rounds

Fatal Dyspnea in a Patient with Renal Failure

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Abstract

A 67-year-old woman with hypertension, diabetes, hypothyroidism and chronic renal failure reported to the hospital for her regularly scheduled hemodialysis, complaining of shortness of breath. Despite fluid removal during her hemodialysis, she remained tachypneic and developed stridor. She was admitted to the hospital for a work-up of a known mediastinal mass, thought to be a goiter. However, she deteriorated over the next several hours and expired. Apost-mortem examination confirmed fatal pulmonary emboli. This case illustrates the fact that, while most patients with chronic renal failure are considered to be at low risk for pulmonary emboli, it is often not diagnosed when present. In this paper, we will review the epidemiological data supporting this notion, examine proposed pathophysiological mechanisms, and review the diagnostic approach that should be considered in the setting of chronic renal failure.
Key Words: Pulmonary embolism, renal failure, CTangiogram, D-dimer.

Case Presentation

A 67-YEAR-OLD WOMAN was admitted to The Mount Sinai Hospital with shortness of breath, wheezing and hoarseness. She had a past medical history of hypothyroidism with a partial thyroidectomy 30 years previously. She also had a known mediastinal mass, presumed to be a goiter, as well as hypertension, diabetes mellitus and end-stage renal disease, for which she was receiving hemodialysis. The patient initially presented for hemodialysis; after the procedure, despite adequate fluid removal, her heart rate was 130 beats/min with both inspiratory and expiratory stridor. She was referred to the emergency department for evaluation of a possible upper airway obstruction.

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She complained of severe shortness of breath, and a family member reported that she had been increasingly lethargic and anorectic during the proceeding two weeks. She was in mild respiratory distress, afebrile and normotensive, with a pulse of 110 beats/min and respiratory rate of 32 breaths/min; oxygen saturation on room air was 90% by oximetry and increased to 96% with two liters of nasal oxygen. A chest radiograph confirmed an approximately 10 x 6 cm mediastinal mass with deviation of the trachea to the right. There were no pulmonary infiltrates or effusions. The ear nose and throat (ENT) physician did not find significant upper airway compromise.

The patient was admitted to the hospital at 3 AM. Her medications included doxazosin, lisinopril, pravastatin, folate, calcium, vitamin D, ducosate and erythropoietin. Her hemoglobin was 10.5 g/dL, hematocrit 32 and platelet count 252,000/mm^3. Plasma potassium was 5.5 meq/L, and an electrocardiogram showed a sinus tachycardia with right atrial enlargement and left ventricular hypertrophy. At 3:45 AM, she complained of severe abdominal pain. She was noted to have pale, clammy skin. The blood pressure and pulse rate were not recorded. Her oxygen saturation fell to 86% by oximetry with 2 L of nasal oxygen. She was treated with oxygen by face mask, and nebulized albuterol. However, at 4:42AM she was found unresponsive and pulseless in her chair, and resuscitative efforts were begun. She was pronounced dead at 5:06 AM.

Autopsy demonstrated pulmonary embolism in the right lower lobe and left upper lobe, with associated pulmonary infarction. The infarct had not been recognized on an emergency room portable chest x-ray. She had atherosclerosis of the superior mesenteric artery with acute thrombosis, severe triple vessel coronary artery disease and left ventricular hypertrophy. A large posterior mediastinal goiter with no tracheal compromise was also found.

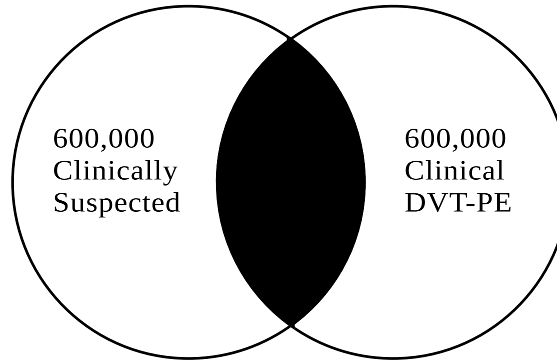

Fig. 1. Venn diagram of clinical suspicion vs. clinical occurrence. Approximately two-thirds of incidents of venous thromboembolism are asymptomatic. Two-thirds of patients presenting with typical signs and symptoms of DVT do not have the disease, which contributes to a low sensitivity and specificity of clinical diagnosis. Adapted with permission from: Wheeler HB, Anderson FA. Venous thromboembolism: Risk factors and prophylaxis. Clin Chest Med 1995; 16(2):235 – 251 (44).

Discussion

Life can only be understood backwards; but it must be lived forwards.

Kierkegaard

This patient illustrates the difficulty in making the diagnosis of deep venous thrombosis-pulmonary embolism (DVT-PE). First, in order to diagnose DVT-PE one must rank it high on the list of differential diagnoses. Second, once a diagnosis of pulmonary embolism (PE) is considered, the physician must rapidly, safely and accurately confirm and treat it in order to make a significant impact on mortality (1). Patients with renal failure have uniquely difficult diagnostic and therapeutic problems. Clinically significant PE is considered rare in patients with renal disease, and some epidemiological data support this clinical impression.

Epidemiology

The incidence of pulmonary embolism in the United States is estimated to be 600,000 cases per year, with an overall mortality of 30% (2, 3). DVT-PE is overdiagnosed for some patients and unsuspected in others (Fig. 1), leading to expensive, misdirected diagnostic evaluations for the former, and greater morbidity and mortality for the latter. The incidence of PE in patients with chronic renal failure is reported to be lower than that in the general population (4). Furthermore, the incidence of clinically significant PE in patients treated with dialysis is considered to be quite low (5). Mossey (4) reported an autopsy series of 2,255 adults from 1969 – 1981. Chronic renal failure was defined as a serum creatinine level greater than 5 mg/dL for six months or renal failure requiring long-term dialysis. The overall incidence of PE in this series was 32.3% (Table 1). Patients with chronic renal failure had an overall incidence of pulmonary emboli of 9.47% ($p<0.0005$) (Table 2). Significantly, all of the emboli in the renal failure group were "microscopic," with no major emboli being identified. This is in sharp contrast to the general population, where 18.4% had microscopic emboli, 4% had macroscopic emboli and 9.9% had both (Table 1). These findings must be compared to multiple autopsy series in which the incidence of PE has ranged from 6 – 64% (6 – 9). The clinical importance of these emboli, based on autopsy series, is difficult to establish; however, Dalen (1) estimated that at least 10% of those deaths were solely attributable to DVT-PE.

Pathogenesis

An accurate assessment of risk factors is an important first step in the evaluation of patients suspected of having DVT-PE. A differential distribution of these risk factors probably explains the reported difference in incidence of DVT-PE in the general population compared to patients with renal failure. Virchow's triad of "stasis" of blood flow, "intimal injury" and the "hypercoagulable" state remains the cornerstone of our understanding of the pathogenesis

TABLE 1
Incidence of Pulmonary Emboli in an Autopsy Population

Age group Yr	n	Microscopic only n (%)	Macroscopic only n (%)	Microscopic and macroscopic n (%)	Total n (%)
18 – 29	42	11 (26)	0 (0)	4 (10)	15 (36)
30 – 39	67	11 (16)	0 (0)	4 (6)	15 (22)
40 – 49	181	37 (20)	4 (2)	12 (7)	53 (29)
50 – 59	464	78 (17)	20 (4)	41 (9)	139 (30)
60 – 69	568	117 (21)	19 (3)	47 (8)	183 (32)
70 – 79	578	103 (18)	31 (5)	64 (11)	198 (34)
>80	355	59 (17)	17 (5)	52 (15)	128 (36)
Total	2,255	416 (18)	91 (4)	224 (10)	731 (32)

n = number
Data from Mossey RT, Kasabian AA, Wilkes BM, et al., modified with permission (4).

TABLE 2
Incidence of Pulmonary Emboli in Chronic Renal Failure

Age group (years)	Patients with renal failure n	Microscopic emboli %
18 – 29	2	0
30 – 39	9	11
40 – 49	13	15
50 – 59	24	8
60 – 69	18	11
70 – 79	21	5
>80	8	18
Total	95	9

n = number of patients
No macroscopic emboli were identified.
Data from Mossey RT, Kasabian AA, Wilkes BM, et al., modified with permission (4).

TABLE 3
Risk Factors for 1,231 Patients with a Diagnosis of Acute DVT and/or PE

Risk Factor	%
Age ≥ 40 years	88.5
Obesity	37.8
History of venous thromboembolism	26.0
Cancer	22.3
Bed rest ≥ 5 days	12.0
Major surgery	11.2
Congestive heart failure	8.2
Varicose veins	5.8
Fracture (hip or leg)	3.7
Estrogen treatment	2.0
Stroke	1.8
Multiple trauma	1.1
Childbirth	1.1
Myocardial infarction	0.7
One or more risk factors	96.3
Two or more risk factors	76.0
Three or more risk factors	39.0

Data from Anderson FA, Jr, Wheeler HB, reprinted with permission (42).

of venous thromboembolism and defines the risks. Table 3 outlines known risk factors for DVT-PE, and all presuppose Virchow's three basic pathogenetic mechanisms. When there is no identifiable risk factor, it is unusual for a patient to develop venous thromboembolism. There is also convincing evidence that risk increases in direct proportion to the number of predisposing factors (10). In the retrospective review by Mossey (4), not all the known risk factors were accurately documented. The prevalence of cancer and atherosclerotic heart disease are two known risk factors for DVT-PE that were recorded but did not account for the difference observed. Other risk factors, such as prolonged bed rest, congestive heart disease and peripheral vascular disease, were not even described. However, patients with renal failure and other co-morbid conditions such as nephropathy, myopathy and diabetes would be thought to have an increased risk for PE. This suggests that uremia, unlike other chronic illness, "protects" the patient from the development of DVT-PE. The most favored explanation for the presumed decrease in DVT-PE in patients with renal failure is abnormalities of the coagulation system.

Many patients with renal failure have venous "stasis," due to their high known incidence of peripheral vascular disease, autonomic dysfunction and diabetes. *In vivo* studies suggest that “intimal injury“ impairs the regulation of vascular tone by nitrous oxide (11). Chronic oxidant stress and/or low antioxidant levels (12) may also contribute to the high prevalence of vascular disease secondary to “intimal injury” in these patients. All of these impairments would predispose these patients to DVT-PE, rather than protect them from it. Certain patients with chronic renal insufficiency have acquired a “hypercoagulable” state (rheumatic conditions with antiphospholipid syndrome, nephrotic syndrome with low antithrombin III levels, etc.), but they may be exceptions to the general population of renal failure patients with lowered DVT-PE risk. Therefore, the observation of a lower incidence of DVT-PE in renal failure patients presents a paradox best explained by examining the coagulation system.

Hemostatic defects in uremia are complex and include thrombocytopenia, minor coagulation abnormalities, and platelet dysfunction. Patients with renal failure are exposed to heparin during hemodialysis, although it is unlikely that systemic anticoagulation sufficient to protect from DVT-PE is ever achieved. Graft occlusion is a common clinical event in hemodialysis patients despite heparin. Furthermore, clot dislodgement from sites of vascular access (bland or septic) is frequently reported as the recognized etiology of emboli when pulmonary embolus is suspected and diagnosed (13, 14). Platelet dysfunction is the most consistently observed abnormality in clotting and is only partially reversed with dialysis. The abnormalities of decreased platelet adherence, aggregation and secretion are best evidenced by a prolonged bleeding time. No uniform pathophysiologic mechanism has yet to emerge to explain these abnormalities. The defects in platelet function have been ascribed to accumulation of guanidinosuccinic acid (15, 16), phenol and phenolic acids (17), uremic middle molecules (18) and nitrous oxide (19). The circulating red cell mass or hematocrit modifies these defects of platelet interaction with endothelium/subendothelium. Therefore, anemia, decreased blood viscosity, and decreased platelet adherence may well be the physiologic factors protecting these patients. Finally, the two studies reporting the lowered occurrence of DVT-PE in patients with renal failure were completed before the widespread use of erythropoietin therapy. Red cell transfusion or improvement of anemia by erythropoietin therapy is associated with decreased bleeding, shortening of the bleeding time and increased platelet adhesion in hemodialyzed uremic patients (20, 21). These effects are dependent both on the increase in red cell mass and on a slight and poorly characterized effect on platelet function that is independent of hematocrit. A recent report of increased fistula thrombosis in a placebo-controlled trial of patients treated with erythropoietin (22) suggests that patients may lose the “protective” effect of anemia and platelet dysfunction and perhaps become hypercoagulable. It is reasonable to conclude that the clinical effect of erythropoietin as a risk factor for DVT-PE remains largely unknown and speculative. Furthermore, the effect of correcting anemia with erythropoietin on the reported low incidence of DVT-PE in renal failure patients deserves further study.

Diagnosis

Acute pulmonary embolism is rarely silent. With appropriate anticoagulant therapy, mortality can be decreased from 30% to less than 10% (23). However, the diagnosis of pulmonary emboli remains difficult (24). In a series of 1276 autopsies of patients who had died of PE, the diagnosis was suspected in only 31.8% of the cases while they were still alive. Paradoxically, the death rate due to DVT-PE has not declined in the last two decades despite new therapies and new diagnostic imaging techniques (25). This can be explained by the mortality of patients whose pulmonary emboli are not suspected and therefore not diagnosed. A review of the epidemiological and physiological data supports the notion of a “lower” risk for clinically significant DVT-PE in uremia. This lower risk factor, however, does not excuse the physician from continued vigilance. Indeed, with the increasing use of erythropoietin, correction of anemia and more aggressive dialytic therapies, this lower clinical risk, on historical series, will need to be re-evaluated.

Once DVT-PE is suspected, there are a number of diagnostic strategies to ascertain its presence. The PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study (26) remains the most complete prospective investigation of PE diagnosis. It accurately quantifies the diagnostic accuracy of ventilation-perfusion (V/Q) scanning, highlights the role of clinical assessment in decision making and scan interpretation, and reaffirms the safety and accuracy of pulmonary angiography. The PIOPED study also underscores the limitation of an indeterminate (i.e., nondiagnostic) scan.

However, since the publication of this landmark study and the introduction of new diagnostic tests, the diagnostic algorithm is changing. These new tests include dynamic contrast-enhanced computerized tomographic (CT) angiography, plasma D-dimer, and magnetic resonance angiography (MRA).

Extensive discussion of pulmonary embolic disease in the medical literature, combined with evidence-based decision analysis, fail to completely define clinical practice guidelines. Moser summarized the problem best (27): "Clinicians dealing with thromboembolism do not work in the literature. They work with specific patients in specific facilities with specific colleagues." Any algorithm utilizing one of the many diagnostic tests must consider these "local" factors. Many of the techniques employed depend on both operator experience (pulmonary angiography, duplex Doppler) and subjective interpretation (V/Q scanning, conventional and CT angiography). Unfortunately, technological advances (multi-slice CT scanning or MRA) are deployed and accepted before they are vigorously studied. Despite these difficulties the medical literature is replete with reasonable diagnostic strategies that can be employed with high sensitivity and specificity when used by an experienced clinician. Fig. 2 represents a typical diagnostic algorithm.

The determination of plasma D-dimer levels has been positioned as an important, early test for diagnosis of DVT-PE. Numerous reports suggest the considerable diagnostic value of plasma D-dimer levels as an indicator of active thrombosis. Van Beck et al. (28) concluded that the D-dimer ELISA assay may have a role in the exclusion of pulmonary embolism in symptomatic outpatients, where its application may reduce the need for angiography by 30% and overall medical costs by 10%. Subsequent studies using rapid (latex) D-dimer tests, which are more clinically practical, seem to confirm these results. This would position plasma D-dimer determinations as an early screening test performed upon clinical presentation of DVT-PE. D-dimer determination is widely available but remains unproven in large-scale trials, and skepticism persists (29). Wells et al. (30) argue that a simple clinical prediction model combined with D-dimer determination may safely exclude PE in a large proportion of patients for whom the diagnosis is suspected. A systematic review by Becker has been used to estimate the sensitivity and specificity of D-dimer tests (31). The reported sensitivity ranged from 48 – 96%

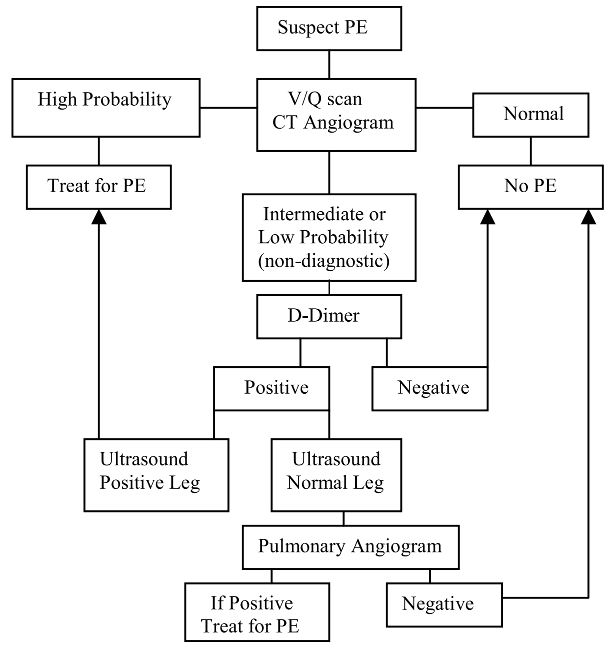

Fig. 2. *D-dimer (+) is above, D-dimer (-) is below critical threshold for exclusion of DVT-PE. Omit the D-dimer in cases of high clinical suspicion, systemic illness, or more than three days from embolism event. CT angiogram may be a substitute for ventilation/perfusion (V/Q) scan or it may follow a nondiagnostic V/Q scan. An abnormal leg ultrasound (US) or echocardiographic evidence of right ventricular hypokinesis justifies treatment without further diagnostic evaluation.

with latex test and from 88 – 100% with ELISA test. The specificity ranged from 21 – 100% with latex test and from 10 – 68% with ELISA test. Overall, in this review, the ELISAs had greater sensitivities but lower specificities than latex. No one D-dimer test has emerged as the best. A critical review of the collective medical literature suggests that a negative D-dimer assay may be most useful, in combination with other studies, to exclude a thrombotic process.

The D-dimer determination in patients with renal disease offers a unique problem. Paradoxically, despite the known coagulation defects of uremia and chronic renal insufficiency, many studies provide evidence of plasma hypercoagulability in hemodialysis patients. This is evident, particularly in the setting of hypertension, diabetes, proteinuria and inflammatory vasculopathy. Plasma D-dimer levels are routinely elevated in patients with chronic renal failure (244 ± 31 μg/L) and diabetic nephropathy (308 ± 74 μg/L) when compared to a control population (96 ± 13 μg/L) without renal disease. Epidemiological data (4, 5) suggest that these higher levels do not imply increased risk for the development of DVT-PE. As the usefulness of plasma D-dimer is in its negative predictive value, it is unclear whether the sensitivity and specificity for this assay determined from a general population of outpatients applies to this specific subgroup. It would seem that the plasma D-dimer would be less useful in excluding DVT-PE in this population of patients, although the validity of this assay and its utility in this group are largely unknown.

The PIOPED study clearly demonstrated the diagnostic sensitivity and specificity of V/Q scanning (Table 4). V/Q scanning remains the procedure of choice for the diagnosis of pulmonary emboli. However, pretest clinical suspicion plays a major role in establishing the diagnosis of PE. Normal, high probability and low probability scans with low clinical suspicion provide accurate clinical assessments upon which sound clinical decision making can proceed. Regrettably, in the PIOPED study, only 27% of the patients had imaging studies adequate for definitive clinical decision making. The primary challenge resulting from the PIOPED data is the need to develop diagnostic strategies for the high proportion of intermediate (nondiagnostic) scans. This is particularly true given the general reluctance of physicians to perform pulmonary angiography despite evidence that it is a safe procedure with excellent diagnostic accuracy. Patients with renal insufficiency not on dialysis are an exception and require alternative diagnostic tests.

A simple strategy for patients with indeterminate, nondiagnostic V/Q scans is based on the observation (32) that patients with documented PE have a high prevalence of deep venous thrombosis (DVT) (82%). Study (Doppler, impedance plethysmography) of the deep venous system and confirmation of DVT would upgrade the finding of an indeterminate V/Q scan and obligate treatment without further need for diagnostic evaluation. Doppler ultrasound has been used to determine venous patency for more than 20 years. Barnes et al. published a series of symptomatic patients in 1975 and 1976 (33, 34), which demonstrated that Doppler examination of the lower extremity was 94% accurate when compared to venography, with a 6% false positive rate. The combination of a negative duplex Doppler study and a plasma D-dimer level below threshold value support a high negative predictive value (95%) for the absence of DVT-PE. Therefore, patients strongly suspected clinically to have PE, but with a nondiagnostic V/Q scan, a D-dimer level with high negative predictive value and a negative duplex Doppler can be followed conservatively.

Recent advances in thoracic cross-sectional imaging have led to great interest in the development of reliable, accurate techniques for diagnosing PE. There has been enthusiasm for dynamic, contrast-enhanced, spiral (helical) CT angiography, because it is quick, accessible and relatively noninvasive. Additional diagnostic information, not available from V/Q scanning, can be gained with CT techniques; it can be diagnostic of nonembolic disease. Several studies report high sensitivity and specificity for determination of pulmonary emboli with spiral CT (35–38). Spiral (helical) CT scanning is generally regarded as excellent for visualization of clots within central or segmental arteries. Critics point out major limitations, including failure to visualize subsegmental arteries (of questionable clinical significance), breathing artifact, and a high incidence of “nondiagnostic” scans. New generation scanners and multislice technologies should eliminate some of these criticisms. Table 5 shows the relative

TABLE 4
PIOPED Data — Pulmonary Embolism Status

	Clinical Science Probability (%)							
	80–100%		20–79%		0–19%		All Probabilities	
Scan Category	n with PE / N	%	n with PE / N	%	n with PE / N	%	n with PE / N	%
High probability	28/29	96	70/80	88	5/9	56	103/118	87
Intermediate probability	27/41	66	66/236	23	11/68	16	104/345	30
Low probability	6/15	40	30/191	16	4/90	4	40/296	14
Near normal/normal	0/5	0	4/62	6	1/61	2	51/128	4
Total	61/90	68	170/569	30	21/228	9	252/887	28

n = number of patients, N = number in group
PE indicates angiogram reading that shows pulmonary embolism or positive determination by committee review.
Data from PIOPED Investigators, modified with permission (26).

TABLE 5
Spiral CT versus Angiography

Investigators	n	Sensitivity (%)	Specificity (%)
Remy-Jardin et al. (1992) (35)	42	100	96
Goodman et al. (1995) (37)	20	86*	92*
	63	89	
Remy-Jardin et al. (1996) (38)	75	91*	78
Drucker et al. (1998) (36)	47	60	81
Interpreted by 2 groups		53	97

n = number of patients
* For central pulmonary emboli. Other percentages are for all pulmonary emboli
Data from Holbert JM, Costello P, Federle MP, modified with permission (43).

sensitivity of spiral CT compared to conventional pulmonary angiography in 4 studies. Sensitivity ranges from 53–100% and specificity ranges from 78–97%. When only central and segmental artery clots are evaluated, sensitivity and specificity are approximately 90% in most studies. However, no large-scale outcomes study similar to PIOPED exists. Most of the patients examined are in a highly selected population with motivated radiologists; results with less highly selected patient population may not be comparable. Woodard (39), in her editorial following publication of early CT trials, suggests that the high sensitivity and specificity may be misleading, and urges caution. Although nominally less invasive than angiography, the radiocontrast dose is significant and, therefore, equally problematic in patients with renal failure not on dialysis. Finally, a nondiagnostic CT angiogram may require further dye exposure (pulmonary angiogram) and cause delay in diagnosis.

Concerns about contrast-induced worsening of renal failure and the need for postcontrast dialysis for patients on chronic hemodialysis are a major impediment to the diagnosis of DVT-PE in patients with chronic renal insufficiency. Magnetic resonance imaging (MRI) and MRA have been employed, but initial results were poor because of respiratory-motion artifact and poor contrast between flowing blood and emboli. The use of faster magnetic resonance hardware combined with dynamic gadolinium enhancement now allows for high resolution imaging in a single breath-hold. Preliminary results are promising (40, 41); however, more studies are needed to identify accurately the sensitivity and specificity of this technique in comparison to other imaging technologies. MRA may be a reasonable first step in diagnosing pulmonary embolus in renal-failure patients in whom contrast may be contraindicated.

Summary

"Be careful to get out of an experience all the wisdom that is in it; Not like that cat that sits down on a hot stove. She will never sit down on a hot stove lid again …and that is well; But also she will never sit down on a cold one anymore."
Mark Twain, *Huckleberry Finn*

The case reviewed here demonstrates that suspicion for PE must be maintained despite the notion and assertion that chronic renal failure patients are at low risk for DVT-PE. This is surprising, considering the chronic nature and co-morbid diseases associated with chronic renal failure. Furthermore, certain markers of plasma hypercoagulability would suggest increased rather than diminished risk. Defects in hemostasis, specifically in platelet function, may explain this paradox. This risk may also be increased with the introduction of erythropoietin to raise hematocrit levels. Diagnosis remains difficult, particularly in patients with renal diseases. Newer and less invasive techniques offer some promise for achieving a definitive diagnosis but must be used with an appreciation of their limitations.

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