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Case Report

Negative D-dimer in idiopathic pulmonary vein thrombosis: a case report and literature review

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Abstract: Pulmonary vein thrombosis (PuVT) is a rare but life-threatening thrombotic disease, mostly caused by operation and cancer, while idiopathic PuVT (iPuVT) is rarely reported. Here we presented a 73-year-old man coming for progressive chest pain and dyspnea due to a thrombus occurred in left lower pulmonary vein detected by coronary CTA. After excluded all known causes of PuVT, he was finally diagnosed as iPuVT. Further a systematic review of iPuVT had been conducted to explore their clinical characteristics, and it is unexpected to find that D-dimer were all negative in iPuVT except those complicated with pulmonary artery embolism or myocardial infarction. Therefore, a negative D-dimer cannot reliably exclude iPuVT.

Keywords: Pulmonary vein thrombosis, rare disease, systematic review, D-dimer

Introduction

Pulmonary vein thrombosis (PuVT) is a rare thrombotic event, presenting with dyspnea, chest pain or hemoptysis, mostly recognized as a potentially fatal early complication of lung transplantation [1], with a high number of systemic embolic events, shock and death [2]. Except lung transplantation, PuVT was also attributed to lobectomy [3], heart transplants [4], cancer [5], radiofrequency ablation [6], trauma [7], severe infection [8] and chronic atrial fibrillation [9]. Nevertheless, a few cases occurred without any known causes, called as idiopathic pulmonary vein thrombosis (iPuVT). Here we presented a case of iPuVT with a systematic review to explore its characteristics.

Case report

A 73-year-old man presented with progressive chest pain and dyspnea without fever, cough, and hemoptysis. The patient was a generally healthy, no medical record before. Except tachypnea, the remaining physical exams revealed normal. Laboratory examinations showed normal arterial blood gas, myocardial enzymes, D-dimer, ECG, and transthoracic echocardiogram. 3 days later, a coronary CTA incidentally found part of a filling defect in left lower pulmonary vein (LLPV) extending into the left atrium suggesting a thrombus, with moderate stenosis of the left main and right coronary arteries (**Figure 1**). Acute myocardial ischemia was excluded because of normal EKG and myocardial enzymes. Subsequently, the patient was diagnosed with PuVT. Anticoagulation therapy was executed immediately with 4100 U low-molecular-weight heparin twice a day for the first 2 weeks, and then 5 mg/day warfarin (INR aim at 2-3). Further exams such as tumor markers (including CEA, CA125, CA199, AFP, NSE, SCC) and positron emission tomography/CT were performed, but no evidence of cancer or other active diseases were found. Hence, all known causes were excluded. Two months later, the patient was symptom free, and a new CT displayed the thrombus in LLPV partly resolved compared with the original image and no longer extended into left atrium (**Figure 2**).

Discussion

It is known that D-dimer is a high sensitive marker for hypercoagulability and is linked with arterial as well as venous thrombotic events. As

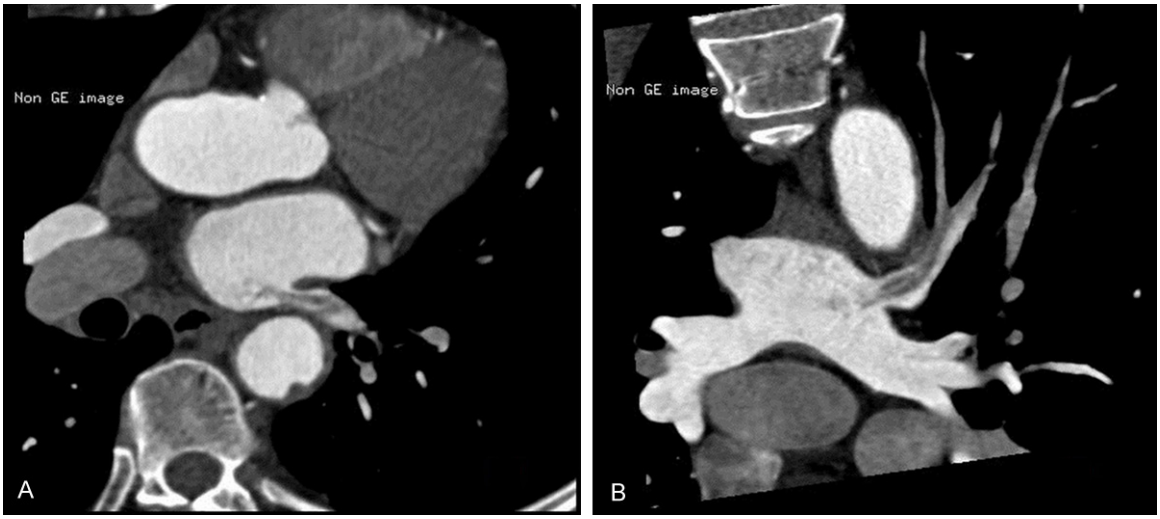

Figure 1. Coronary computed tomography angiography (CTA). A: A large filling defect in the left lower pulmonary vein (LLPV) that extended into the left atrium. B: The thrombus in the LLPV that descended into the distal veins.

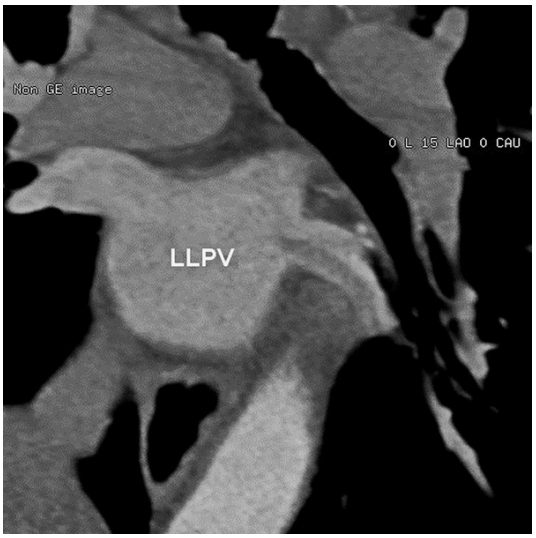

Figure 2. Computed tomography angiography scan 2 months after anticoagulation therapy. The thrombus remained in the LLPV but did not extend into the left atrium and was partly resolved.

a high negative predictive value, D-dimer plays a critical role in exclusion of pulmonary thrombosis. To understand the role of D-dimer in idiopathic pulmonary vein thrombosis, we conducted a systematic review. Two authors (YC. Y and L. Z) independently searched the PubMed, Cochrane, and Embase from their earliest records to December 2015 using "pulmonary + vein/venous + thrombosis/embolism/thromboembolism" as the key words. The included studies were reviewed according to PRISMA guidelines (diagram in **Figure 3**), must report at least 1 case of iPuVT, being limited to humans and in English. Repetitively cited cases in different papers were also excluded.

The literature search identified 126 relevant articles, in which 12 no case report, 9 duplicate cases, and 8 other pulmonary vein related diseases were eliminated. Secondly we excluded paper with known causes, including cancer, surgery, atrial fibrillation, radiofrequency ablation, compression of pulmonary vein, severe infection and hypercoagulation or recent thrombosis in 6 months; other 4 controversial cases by two authors were also eliminated as no claim of iPuVT in the articles. Finally, 21 cases of iPuVT (20 cases [10-29] plus our case) were summarized in Supplementary Table 1.

There were 5 females and 16 males, for a male/female ratio of 3.2. Patient ages ranged from 15 to 82 years, average: 63.9 years. In all 21 cases, 15 patients complained of chest pain (76.2%) and 5 dyspnea/shortness of breath (23.8%), 2 cough (9.5%), 2 abdominal pain. iPuVT occurred in LLPV in approximate half of patients (10/21, 47.6%), different from previous study where LUPV (8/26, 30.8%) was most common in non-surgery patients [2], but only 3 in LUPV (14.3%) in iPuVT, and 9/21 (42.9%) thrombus had extended into the left atrium. 13 cases reported the result of D-dimer, in which only 2 cases were positive (21.4%), including 1 case complicated with right pulmo-

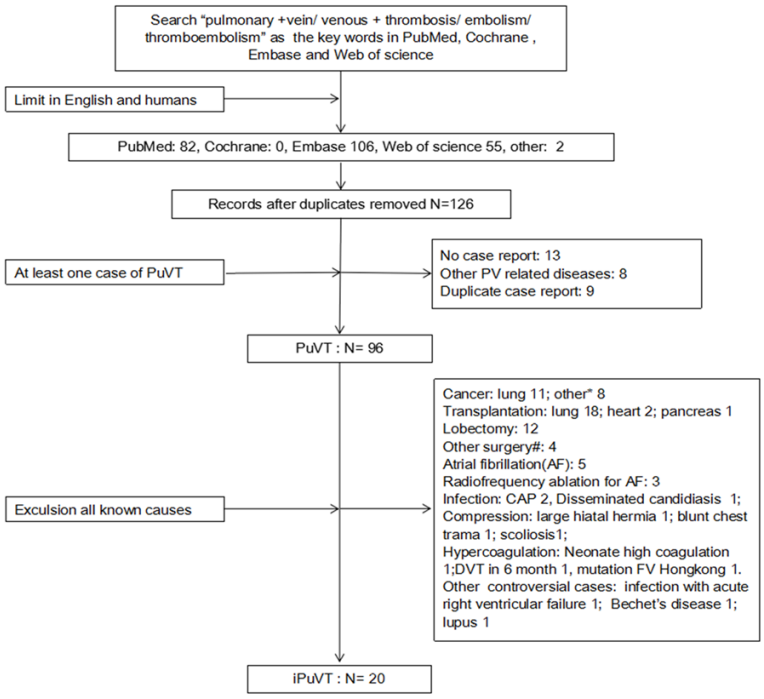

Figure 3. Selection process for systematic review of literature. CAP: community acquired pneumonia, PuVT: pulmonary vein thrombosis, iPuVT: idiopathic pulmonary vein thrombosis, *metastatic choriocarcioma, carcinoma esophagus, liposarcoma, advanced parotid gland adenocarcinoma, pancreatic adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, tumor testis. #Abdominal hysterectomy, cardiosurgery, cesarean section, transjugular intrahepatic porto-systemic shunt.

nary artery embolism and another acute anterior-lateral myocardial infarction, thus D-dimer were totally negative in iPuVT if excluding other thrombus complication. Except for 4 cases no mention the therapy, 14 patients were treated by anticoagulation, 2 by surgery, and 1 by antiplatelet. 12 patients have recovered in 13 cases mentioned outcome, another one has collapsed after anticoagulation and no further prognosis.

In contrast to our imagination, all of iPuVT is negative for D-dimer, except those complicated with pulmonary artery embolism or myocardial infarction. D-dimer antigen can exist on fibrin degradation products derived from soluble fibrin before its incorporation into a fibrin gel, or after the fibrin clot has been degraded by plasmin [30]. Many factors might affect the sensitivity and specificity of D-dimer, including the extent of thrombosis and fibrinolytic activity, duration of symptoms, anticoagulant therapy, comorbidity, inflammatory diseases, cancer, elderly age, pregnancy and the postpartum period [31]. We suspect that iPuVT is caused by the local vascular epithelial cell damaged, following by thrombosis in situ. Different to pulmonary artery embolism, iPuVT has not the movement of exfoliative blood clots from deep vein to pulmonary artery, thus less fragmentation and microthrombosis existing in the peripheral circulation lead to a normal value of D-dimer. Besides, lower blood pressure and flow speed in pulmonary vein may reduce the local fibrinolysis activity and sequentially D-dimer release. However, the value of D-dimer in secondary PuVT is unclear. We guess that D-dimer might be elevated because most of primary diseases can already present a positive value of D-dimer. A few cases supported our hypothesis, high level of D-dimer was detected in one PuVT patient with malignant lymphoma [32], and 2 with positive lupus anticoagulant [33, 34]. It must be point out that the number of iPuVT cases was very small, which limited our ability to precisely explore the clinical characteristics and prognoses.

In conclusion, our report suggests that negative D-dimer cannot reliably exclude PuVT, especially in iPuVT. We look forward further study to find out a valuable coagulative-fibrinolytic marker in diagnosis and evaluation of iPuVT.

Disclosure of conflict of interest

None.

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Supplementary Table 1. The detail characteristics of including study

Case report	Ref	Sex	Age	Symptom	Location	Extending into LA	Other thrombus*	Past medical history	Treatment	Evaluation	D-Dimer
2015 takeuchi	[8]	M	82	Chest pain	RLPV	N	N	Decreased CVRR value, HTA, dyslipidaemia	Anticoagulation	Recovered	Normal
2015 Takeuchi	[9]	M	78	Chest pain	LLPV	Y	N	Aspirin 82 mg for antiplatelet therapy	No mention	No mention	Normal
2015 Takeuchi	[10]	M	76	Chest pain	LLPV+LUPV	Y	N	None	No mention	No mention	Normal
2015 Takeuchi	[11]	M	68	No mention	LLPV	N	N	No mention	Anticoagulation	Collapsed	No mention
2015 Takeuchi	[12]	F	72	Chest pain	RLPV	Y	N	50% stenosis in the left anterior descendant	No mention	No mention	No mention
2014 Mitra	[13]	M	70	Dyspnea, chest pain, cough	LLPV	N	N	COPD, tobaccoabuse, hypertension	Anticoagulation	No mention	Normal
2014 Ozyurt	[14]	F	15	Chest pain, palpitations, shortness of breath	RUPV	Y	Pulmonary artery	None	Anticoagulation	Recovered	3850
2013 Takeuchi	[15]	M	73	Chest pain	LUPV	N	N	Dyslipidemia and asthma	Anticoagulation	Recovered	Normal
2013 Takeuchi	[16]	M	70	Chest pain	LLPV	Y	N	4 stents in coronary artery, 100 mg aspirine	Antiplaquates	No mention	No mention
2013 Sahay	[17]	M	48	Syncope	LLPV	N	N	Diabetes mellitus, hypertension, pancreatic arteriovenous malformation	Anticoagulation	Recovered	Normal
2013 Takeuchi	[18]	F	69	Chest pain	LLPV	N	N	Transient ischaemic stroke, treated with clopidogrel, I AVB,	Anticoagulation	Not dissolve much after 3 months	Normal
2013 Saoraya	[19]	M	68	Increasing intensity of left lower quadrant pain	LLPV	Y	Left renal infarction	Inguinal hernia and herniorrhaphy	Anticoagulation	No mention	No mention
2012 Takeuchi	[20]	M	79	Chest pain	LUPV	N	N	Hypertension	No mention	No mention	No mention
2012 Takeuchi	[21]	M	77	No mention	RUPV	N	N	Lacuna infaraction in the pons	Anticoagulation	Recovered	No mention
2012 Wu	[22]	M	30	Intermittent left chest pain for 6 months	LLPV	Y	N	Hypertension	Surgery	Recovered	Normal
2012 Mumoli	[23]	M	80	Shortness of breath	LUPV	N	N	Coronary artery bypass for previous myocardial infarction and for congestive heart failure	Anticoagulation	Recovered	Elevated
2011 Komatsu	[24]	M	57	Chest pain	LLPV+RLPV	N	N	Dyslipidemia	Anticoagulation and antiplaquetes	No mention	Normal
2009 Alexander	[25]	F	47	Massive hemoptysis with left chest pain and mild dyspnea	LLPV	N	N	No mention	Surgery	No mention	Normal
1999 Selvidge	[26]	F	33	Left sided abdominal pain with nausea and vomiting	RLPV	Y	Spleen infarction	Cigarette smoker and cocaine user	Anticoagulation	Recovered	No mention
2015 Takeuchi	[27]	M	77	No mention	RUPV	N	Lacuna infraction	Aspirin 82 mg for antiplatelet therapy	Anticoagulation	Recovered	No mention
This case		M	73	Chest pain and shortness of breath	LLPV	Y	N	None	Anticoagulation	Recovered	Normal

CVRR: coefficient of variation of the R-wave to R-wave interval, LUPV: left upper pulmonary vein; LLPV: left lower pulmonary vein; RUPV: right upper pulmonary vein; RLPV: right lower pulmonary vein.