

Research Article

Atypical manifestations of pulmonary embolism

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Abstract

Pulmonary embolism (PE) is an age-related disorder which is potentially fatal, but frequently misdiagnosed. However, the true prevalence of pulmonary embolism is unknown. Inaccurate estimates of PE prevalence might, in part, be attributable to underrecognition of atypical presentations of this disorder. If true prevalence is unknown, the positive predictive values of both typical and atypical symptoms and signs of PE will be unreliable. The negative predictive value of those parameters will, likewise, be unreliable. The aim of this review is to make clinicians more aware of atypical manifestations of PE, thereby increasing the likelihood of correct diagnosis and, hence, ascertainment of the true prevalence of PE. The range of atypical manifestations was explored by a literature search, using MEDLINE from 1946 to February 2019, and EMBASE, from 1947 to February 2019, and Pubmed, from February 2014 to February 2019, using the search terms atypical, uncommon, unusual, pulmonary embolism, lung embolism, pulmonary thromboembolism.

This search revealed atypical presenting features such as non pleuritic retrosternal pain, abdominal pain, atypical breathing patterns, pulmonary oedema, Dressler's syndrome, atypical radiographic manifestations, atypical electrocardiographic features, manifestations associated with oxygen saturation of 95% or more, coexistence of acute myocardial infarction and pulmonary embolism, coexistence of thoracic aortic dissection and pulmonary embolism, neurological manifestations other than stroke, paradoxical embolism, acute venous thrombosis of atypical location, and pulmonary embolism with normal D-dimer levels.

Introduction

Clinical decision rules (CDRs) are the building blocks for clinical decision making in pulmonary embolism (PE). They can be used to rule in PE (as in the Wells Rule) or to rule out PE (as in the PERC Rule). In the original Wells formula typical manifestations of PE were deemed to be 2 or more respiratory points (ie new-onset dyspnoea or worsening chronic dyspnoea, pleuritic chest pain, chest pain that is nonretrosternal and nonpleuritic, an arterial oxygen saturation less than 92% while breathing room air that corrects with oxygen supplementation less than 40%, haemoptysis, and pleural rub), and leg symptoms. Other typical manifestations include low-grade fever and results of chest radiography compatible with PE. Atypical manifestations were those that did not belong to the "typical" category [1].

In a subsequent study, Wells, et al. formulated a simplified CDR where the variables (again characterised by typicality for PE) comprised haemoptysis, heart rate > 100/minute, immobilisation or surgery in the past 4 weeks, clinical signs and symptoms of deep vein thrombosis (DVT), malignancy,

and an alternative diagnosis less likely than PE. Using those variables, a total score of > 4 signified that PE was likely [2].

The Pulmonary Embolism Rule out Criteria (PERC) was a CDR formulated to rule out PE in patients perceived to have low probability of PE, the latter on the basis of the clinician's unstructured clinical evaluation. In such patients the aim of the CDR was to rule out PE if all eight of the following criteria were fulfilled:

Age < 50, pulse < 100/minute, SaO₂ > 94%, no unilateral leg swelling, no haemoptysis, no recent trauma or surgery, no prior PE or DVT, and no hormone use [3].

Strict application of PERC criteria generates a 1% prevalence of missed PE [4]. This is rate of missed diagnosis is acceptable, given the fact that a 2% rate of missed diagnosis in the point of equipoise where subjects with a lower rate of missed diagnosis would not be benefited by diagnostic testing [5], or might even be harmed by diagnostic procedures such as computed tomography pulmonary angiography (CTPA) which pose radiation risk and risk of contrast-related renal injury [6].

More Information

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In contrast to the proliferation of CDRs subsequent to Wells, a school of thought has emerged which posits that unstructured clinical impression (so-called “gestalt”) is, at the very least, as reliable as the sole use of CDRs [7]. Vital signs such as respiratory rate (RR) and SaO₂ are available both to CDR and to gestalt. According to one study, respiratory rate of < 21/minute is associated with a 95% negative predictive value for PE [8]. By contrast a SaO₂ of < 95% (whilst breathing room air) is associated with an Odds Ratio of 3.3 (95% Confidence Interval 2.5 to 4.4) in favour of PE [3].

PE can, however, be totally asymptomatic even in patients who have DVT complicated by emboli located in the major pulmonary arteries [9]. The corollary is that, in one study, among 334 subjects with CTPA-validated PE, up to 75.9% of the patients with centrally located pulmonary emboli failed to achieve a “PE likely” score of > 4. In that study there were 7 PE-related fatalities in patients with centrally located emboli, and 3 deaths among patients with segmental emboli. There were no deaths among patients with subsegmental emboli [10].

Atypical manifestations of pulmonary embolism

Typical presenting symptoms and signs usually depicted in CDRs comprise cough, haemoptysis, pleuritic chest pain, non-retrosternal non pleuritic chest pain, new onset dyspnoea, worsening chronic dyspnoea, unilateral leg swelling, and SaO₂ < 95% [1,3,30]. Atypical presenting symptoms and signs are those which do not belong to the typical category. Atypical manifestations can occur in isolation. Alternatively, they may occur in association with typical signs and symptoms.

Retrosternal pain that is non pleuritic

According to Wells, et al. non pleuritic retrosternal pain belongs to a category which is atypical of PE [1]. When non pleuritic retrosternal pain occurs in PE it is attributable, in some cases, to myocardial ischaemia, the latter the outcome of the combination of hypoxemia and increased cardiac work [11]. This presentation can simulate acute coronary syndrome, especially in the presence of elevation in serum troponin levels and concurrent ST segment depression and/or T wave inversion [12]. Diagnostic confusion is compounded by the fact that PE can also present with electrocardiographic (ECG) stigmata simulating ST segment elevation myocardial infarction (STEMI) in the absence of concurrent coronary

artery occlusion [13]. In the latter review of this phenomenon, the STEMI stigmata occurred most frequently in leads V1-V4, less frequently in the inferior leads II, III, and AVF, and least frequently in leads V5 and V6. The diagnosis of PE was validated by CTPA, ventilation/perfusion scintigraphy, angiography, and autopsy, in 6,2,17, and in 8 subjects, respectively. The Wells score for PE amounted to < 2 in 44.4% of the 27 patients in whom that parameter was measured [13].

Exceptionally, PE may coexist with acute myocardial infarction (AMI). This scenario occurs when AMI-related right ventricular mural thrombus is complicated by the occurrence of PE [14]. Conversely AMI may be the outcome of PE-related paradoxical embolism (PDE) [15].

Abdominal pain

Abdominal pain (or flank pain) may be a feature of PE under the following circumstances (Table 1).

(i) Abdominal pain may be the sole manifestation of PE.

This manifestation of PE may be a symptom of acute onset hepatic congestion attributable to PE-related right heart failure [16,17]. In other instances PE-related abdominal pain is believed to be attributable to diaphragmatic irritation resulting from lower lobe pulmonary infarct [18].

(ii) Abdominal pain which simulates abdominal pain attributable to AMI.

This scenario occurs when PE-related abdominal pain is associated with an electrocardiogram which shows ST segment elevation [19,20]. The differential diagnosis of this scenario includes AMI, a disorder in which a study of 94 consecutive subjects with atypical AMI documented a 11% prevalence of abdominal pain among subjects who did not have chest pain [21]. That statistic is fortuitously close to the statistic of a 12% prevalence of abdominal pain among 90 subjects with PE evaluated by Israel, et al. [22].

(iii) PE-related abdominal pain which is attributable to the underlying cause of PE.

This scenario is exemplified by ovarian vein thrombosis, a disorder which may not only be the underlying cause of abdominal pain, but also the underlying cause of PE [23].

Table 1: Pulmonary embolism-related abdominal pain.

First author and reference	Age	Sex	RR	SaO ₂ %	Typical PE symptoms	Comments
Al-Mane [16]	35	F	27	98	Y	Hepatic congestion
Phillipp [17]	21	F	NA	NA	Y	Hepatic congestion
Gantner [18]	48	M	16	99	N	Right lower lobe infarct
Fallahi [19]	54	M	20	92	Y	ST segment elevation
Hodgkinson [20]	20	M	NA	NA	Y	ST segment elevation
Heavrin [23]	29	F	16	100	Y	Ovarian vein thrombosis
Vavuranakis [24]	28	F	31	80	Y	Paradoxical splenic artery embolism
Turedi [25]	73	F	32	NA	N	Paradoxical splenic renal and hepatic artery embolism

KEY: M: Male; F: Female; Y: Yes; N: No; NA: Not Available

(iv) PE - related abdominal pain attributable to paradoxical embolism.

This occurs when PE is complicated by paradoxical embolism involving, the splenic artery [24], or the splenic, renal, and hepatic arteries simultaneously [25].

Abdominal pain is most easily identifiable as being attributable to PE when it is associated with other symptoms of PE such as breathlessness. Diagnostic difficulty occurs when abdominal pain is the sole presenting feature of PE, as was the case in anecdotal reports [26,27] and in 9.5% of forty two PE subjects in a retrospective study conducted in a tertiary hospital [28]. Misattribution of PE-related abdominal pain to a “surgical” cause unrelated to PE can result in inappropriate laparotomy and surgical exploration [16,22].

Atypical breathlessness or atypical breathing pattern

Orthopnoea is atypical of PE. In one study orthopnoea was recorded in only 38% of 97 PE patients who had no prior cardiopulmonary disease [29]. In 19% of 192 PE patients in that study the other atypical feature was a rate of onset of dyspnoea which covered a number of days instead of hours [29]. In a larger study of 1,100 consecutive subjects (age range 15-94) with suspected PE (including 440 with eventual angiographically proven PE) orthopnoea occurred in only 1% of PE subjects, and was significantly ($p = 0.0001$) less common in PE than in non PE. In that study, gradual onset PE occurred in only 3% of PE subjects, and was, also, significantly ($p = 0.0001$) less common in PE than in non PE [30]. According to another study, patients with gradual onset dyspnoea experience significantly ($p < 0.001$) greater delay in having a diagnosis of PE than counterparts with sudden onset dyspnea [31]. Gradual onset dyspnoea is also associated with significantly ($p < 0.001$) greater risk of acquiring a mistaken diagnosis, as shown in 186 PE patients in whom mistaken diagnoses included bronchitis (35%), heart failure (31%), pneumonia (13%), and exacerbation of COPD (8%) [31].

Platypnoea orthodeoxia is the antithesis of orthopnoea.

The clinical hallmark of this syndrome is worsening of breathlessness and worsening of hypoxaemia on sitting up. In the context of PE, this disorder is believed to be attributable to right-to-left shunting of blood through a patent foramen ovale (PFO) as a result of PE-related increase in pulmonary artery pressure [32].

In one study wheezing which had a severity similar to acute severe asthma was an atypical presentation in eleven out of 250 patients with angiographically validated PE [33]. PE-related wheezing is commoner in patients with previous cardiopulmonary disease [34]. Furthermore, asthma, itself, is associated with an increased risk of pulmonary thromboembolism [35]. PE can also atypically present as acute unexplained exacerbation of COPD [36]. In the latter

meta-analysis 68% of emboli were located in main pulmonary arteries, lobar arteries, or interlobar arteries [36].

The “voice box” syndrome is an atypical feature exemplified by a 19 year old nonsmoker woman who subsequently suffered cardiorespiratory arrest attributable to massive PE. The presenting symptom was new-onset hoarseness and sore throat, initially in the absence of breathlessness. At autopsy, the underlying cause of hoarseness proved to be compression of the recurrent laryngeal nerve by a “large thrombotic formation that completely occluded the outflow tract of the pulmonary artery” [37].

Stridor was the atypical presenting feature in a 62 year old man in whom wheezing was an associated symptom. Both symptoms resolved after treatment which included heparin and bronchodilators [38].

PE can also atypically present with hiccups, without intercurrent chest pain or dyspnea [39]. In the latter report, patient 1 had a Wells score of 1.5, patient 2 had a Wells score of 3, and patient 3 had a Wells score of 1.5 [39].

Pulmonary oedema as a manifestation of pulmonary embolism

Bilateral, non-cardiogenic pulmonary oedema has been documented as a manifestation of PE in patients aged 61 [40] and 72, respectively [41]. Unilateral pulmonary oedema was reported in a 54 year old man in whom chest radiography also showed increased lucency in one region of the lung fields (Westermarck’s sign) and prominence of one of the pulmonary arteries (Palla’s sign) [42].

Atypical radiographic signs of PE

Atypical features include lobar consolidation mimicking pneumonia [44]. Other atypical features include cavitation [45], pneumothorax [45], hydropneumothorax [46], pyopneumothorax [47], pneumomediastinum [48], and pulmonary oedema [40-42].

Pleural effusion

Dressler’s syndrome is the association of PE with pericardial effusion [49], typically in a patient with PE-related pleural effusion. When pleural effusions occur in PE, they typically occupy < 50 of the hemithorax. Larger pleural effusions are distinctly atypical [50]. Unusually, as well, PE-related pleural effusions may be loculated [50], potentially simulating those attributable to bacterial pneumonia, especially if associated with pulmonary opacities [50].

Pulmonary embolism with SaO₂ amounting to 95% or more (breathing room air) (Table 2)

A SaO₂ of 95% or more is atypical of PE, both in patients with typical PE symptomatology and in those with atypical symptomatology (Table 2).

Table 2: Pulmonary embolism with SaO₂ of 95% or more.

First author and reference	Age	Sex	RR	SaO ₂ %	Typical PE symptoms	Hiccups	Abdo pain	ST elevation	Giant T waves	Syncope	Seizures	Comments
Larsen [51]	18	F	18	99	Y	N	N	N	N	N	N	Dyspnoea
Kahanov [52]	18	F	28	99	Y	N	N	N	N	N	N	Chest pain
Durning [53]	81	M	20	98	N	Y	N	N	N	N	N	
Mansmann [54]	42	M	NA	97	N	N	Y	N	N	N	N	
Gantner [18]	48	M	16	99	N	N	Y	N	N	N	N	
Hosein [26]	44	M	NA	98	N	N	Y	N	N	N	N	
Rehman [27]	53	M	22	96	N	N	Y	N	N	N	N	
Amesquita [55]	52	M	23	99	Y	N	Y	N	N	N	N	Cough
Boari [56]	67	M	18	97	N	N	Y	N	N	N	N	
Migneault [57]	63	F	20	97	N	N	Y	N	N	N	N	
Heavrin [23]	29	F	16	100	Y	N	Y	N	N	N	N	Pleuritic pain
Sethuraman [58]	14	M	20	99	N	N	Y	N	N	N	N	
Sethuraman [58]	21	M	18	100	Y	N	Y	N	N	N	N	Cough, pleuritic pain
Noble [59]	51	M	32	100	N	N	N	Y	N	N	N	
Falterman [60]	62	M	18	99	Y	N	N	Y	N	Y	N	Dyspnoea
Lee [61]	63	F	16	98	Y	N	N	Y	N	N	N	Chest pain
Pillariseti [62]	55	M	16	97	Y	N	N	N	Y	N	N	Dyspnoea
Alreshq [63]	92	M	16	95	N	N	N	N	N	Y	N	Near-syncope
Lu [64]	21	M	18	95	N	N	N	N	N	N	Y	
Meyer [65]	50	M	NA	100	N	N	N	N	N	N	Y	
Bhatty [66]	60	M	14	95	Y	N	N	NA	N	N	N	Aortic dissection
Al-Zuabi [67]	70	F	NA	100	NA	N	NA	NA	NA	N	N	Aortic dissection
Tomaszuk-Kazberuk [68]	69	M	18	96	Y	N	N	Y	N	N	N	Aortic dissection

Key: F: Female; M: Male; RR: Respiratory Rate; SaO₂: Oxygen saturation on room air; PE: Pulmonary Embolism; N: No; Y: Yes; NA: Not available; Abdo: abdominal

Atypical PE-related symptomatology associated with SaO₂ of 95% or more

(i) This was exemplified by an 18 year old woman who presented with sudden worsening of dyspnoea on minimal exertion. Her pulse rate was 52-56/minute, RR 18 breaths/minute, SaO₂ amounting to ninety nine percent whilst breathing room air. Computed tomography pulmonary angiogram showed a large embolus in the main pulmonary trunk extending into both the right and left pulmonary arteries [51].

(ii) In another report, an 18 year old woman presented with chest pain and abdominal pain. Her RR was 28 breaths/min, and her SaO₂ was 99% (breathing room air). CTPA showed bilateral basilar segmental and sub segmental filling defects consistent with PE [52].

Atypical PE-related symptomatology associated with SaO₂ of 95% or more.

(a) PE-related hiccup with SaO₂ of 95% or more

This was exemplified by an 81 year old man who presented with hiccup, and also without concurrent dyspnoea or abdominal pain. His RR was 20 breaths/minute, SaO₂ 98% (breathing room air). CTPA showed an embolus in the anterior and lateral segments of the left lower lobe pulmonary artery [53].

(b) PE-related abdominal pain with SaO₂ of 95% or more

(i) This was a 42 year old man who complained of right flank and lower abdominal pain. SaO₂ was 97% (breathing

room air). CTPA revealed an embolus in the lower branch of right lower lobar pulmonary artery [54].

(ii) In another report a 48 year old man presented with right upper quadrant abdominal pain. His RR was 16 breaths/minute, SaO₂ 99% breathing room air. CTPA showed a large central embolus in the right main pulmonary artery [18].

(iii) This was a 44 year old man with right upper quadrant abdominal pain and no dyspnoea. SaO₂ amounted to 98% breathing room air. CTPA showed an embolism involving the right posterior segmental arteries [26].

(iv) A 53 year old man complained of lower right back pain radiating to the right upper quadrant of the abdomen. He denied chest pain or dyspnoea. His RR was 22 breaths/minute, SaO₂ 96% (breathing room air). CTPA showed an embolus in the segmental branch of the right lower lobe [27].

(v) A 52 year old man complained of right flank pain in association with right upper quadrant pain. He also complained of dry cough. His RR was 23 breaths/minute, SaO₂ 99% breathing room air. CTPA showed pulmonary emboli in the segmental branches of the right lower lobe pulmonary artery [55].

(vi) A 67 year old man complained of left flank pain radiating to the left upper quadrant of the abdomen. His RR was 18 breaths/minute, SaO₂ 97% (breathing room air). CTPA showed occlusion of the lower branch of the right pulmonary artery [56].

(vii) A 63 year old woman complained of right upper

quadrant abdominal pain worsened by breathing. She denied chest pain or dyspnoea. Her RR was 20 breaths/min, SaO₂ 97% (breathing room air). PE was initially thought to be unlikely, but she subsequently deteriorated. A subsequent CTPA showed bilateral extensive pulmonary embolism [57].

(viii) A 29 year old woman presented with a history of abdominal pain which subsequently proved to be attributable to ovarian vein thrombosis. Her RR was 16 breaths/min. SaO₂ was 100% on room air. Her CT scan was “diagnostic of pulmonary embolism” [23].

(ix) A 14 year old boy complained of left sided abdominal pain, His RR was twenty breaths/min, SaO₂ 100% breathing room air. CTPA showed bilateral lower lobe PE [58].

(x) A 21 year old man complained of left upper quadrant abdominal pain. His RR was 18 breaths/min. SaO₂ was 100% (breathing room air). CTPA revealed a “large left and small right PE and left lower lobe infarct” [58].

(c) PE-related ST segment elevation in association with SaO₂ 95% or more.

(i) The work up of a 51 year old man with a history of recent transient hypotension included an ECG which showed ST segment elevation in leads V1-V3. His RR was 32 breaths/min, SaO₂ 100% on room air. CTPA revealed a large saddle embolus extending from the pulmonary trunk into all branches of the right pulmonary artery, “resulting in markedly decreased blood flow to the entire right lung” [59].

(ii) A 62 year old man presented with a history of syncope and acute onset dyspnoea. His RR was 18 breaths/min, and his SaO₂ was 99% on room air. His ECG showed ST segment elevation in leads V1 to V4. He subsequently became haemodynamically unstable and died. Autopsy revealed that he did not have AMI, but that he had died of pulmonary embolism [60].

(iii) A 63 year old woman presented with a history of central chest pain cough. Her RR was 16/min and SaO₂ was 98% on room air. Her ECG showed progressive concave ST segmentation in the anterior leads, and her Wells score indicated low probability of PE. A subsequent CTPA showed multiple right-sided pulmonary emboli [61].

(d) PE-related “giant” T wave inversion associated with SaO₂ 95% or more.

A 55 year old man complained of mild aching chest discomfort and exertional dyspnoea for a week. His RR was 16 breaths/min, SaO₂ was 97%. His ECG showed giant T wave inversion simulating high-grade stenosis of the proximal left anterior descending artery. CTPA showed large bilateral emboli that were partially occlusive of both main pulmonary arteries [62].

(e) PE-related near-syncope with SaO₂ of 95% or more

A 92 year old man presented with a history of light-headedness followed by a fall. His ECG showed sinus bradycardia (heart rate 48 beats/min) and first degree atrioventricular block. His respiratory rate was 16 breaths/min, and his SaO₂ was 95%. A ventilation/perfusion scan showed evidence of a high probability PE with involvement of > 50% of the pulmonary vasculature [63].

(f) PE-related seizures and SaO₂ of 95% or more.

(i) A 21 year old man gave a history of two recent episodes of convulsions and recent onset dyspnoea. His RR was 18 breaths/min and his SaO₂ was 95% on room air. Transthoracic echocardiogram showed marked dilatation of the right ventricle and right atrium, moderate -to-severe tricuspid regurgitation, and elevation of pulmonary artery systolic pressure to 82 mm Hg. CTPA showed “filling defects over bilateral pulmonary arteries” [64].

(ii) A 50 year old man presented with a history of seizures, but no history of dyspnoea or chest pain. SaO₂ was initially 100% except for a brief spell of tachycardia followed by bradycardia and a brief spell of SaO₂ in the 80s range. Transthoracic echocardiography showed an increase in pulmonary artery pressure, thereby raising the index of suspicion for PE. Ventilation/perfusion scan showed multiple areas of mismatch. He subsequently experienced cardiopulmonary arrest and died. Autopsy showed a saddle pulmonary embolism and massive bilateral emboli [65].

(g) Coexistence of PE and dissecting aortic aneurysm in the presence of SaO₂ of 95% or more.

Three patients, aged 60, 69, and 70, respectively, had PE coexisting with dissecting thoracic aortic aneurysm. Their corresponding SaO₂ levels (on room air) were 95%, 100% and 96%, respectively. Data on these three patients [66-68], and six others with the association of PE and dissecting thoracic aortic aneurysm are depicted in table 3.

Atypical electrocardiographic stigmata of pulmonary embolism

Typical ECG stigmata of PE include sinus tachycardia, S1Q3T3 configuration, T wave inversion in leads V1-V4, RBBB, and supraventricular tachyarrhythmias [69]. A Qr pattern in V1 signifies poor prognosis [70]. Atypical features include sinus bradycardia [51], ST segment elevation simulating STEMI [13], “Giant” T wave inversion in leads V1-V4 [62], LBBB [71], Brugada pattern [72,73], CHB [74], ventricular fibrillation [75], and pulseless electrical activity [75], the latter sometimes associated with good outcome if its underlying cause(PE) is promptly identified and appropriately managed [76].

Atrial fibrillation deserves special mention when PE originates from a right atrial thrombus [77].

Table 3: Coexisting aortic dissection and pulmonary embolism.

First author and reference	Age	Sex	RR	SaO ₂ %	Dyspnoea	Chest pain	Backache	Comments
M'Iudoran [84]	70	M	NA	78	Y	Y	N	D-dimer 18.6 mcg/ml
Tomaszuk-Kazberuk [68]	69	M	18	96	N	Y	Y	DVT common femoral vein
Leu [82]	57	F	NA	NA	Y	N	N	
Ramponi [85]	75	M	NA	NA	Y	Y	Y	Saddle PE
Chai [86]	46	F	NA	NA	N	Y	N	DVT popliteal vein
Bhatty [66]	60	M	14	95	Y	Y	N	DVT right leg
Cruz [87]	71	F	NA	NA	Y	Y	N	
Al-Zuabi [67]	70	F	NA	100	NA	NA	NA	Dementia
Akgul [83]	61	M	NA	NA	Y	NA	Y	DVT right popliteal femoral and iliac veins

Key: F: Female; M: Male; RR: Respiratory Rate; SaO₂: Oxygen saturation on room air; N: No; Y: Yes; NA: Not available

Coexistence of pulmonary embolism and thoracic aortic dissection (Table 3)

Thoracic aortic dissection (TAD) can fortuitously coexist with PE. Misdiagnosis may be attributable to the fact that both disorders may be characterized by chest pain and dyspnea [78], pleuritic pain and haemoptysis [79], and elevation in serum D-dimer levels [80]. Furthermore, a Taiwanese nationwide cohort study showed that, after adjusting for age, sex, and duration of hospitalisation, patients with aortic aneurysms (AA) were associated with a 1.88-fold higher risk of DVT (95% Confidence Interval 1.52 to 2.33) and a 1.90-fold higher risk of PE (95% CI 1.58 to 2.25) compared with the non-AA cohort. The authors hypothesized that this might, in part, be attributable to compression of the superior vena cava leading to venous stasis and heightened risk of thrombus formation [81]. Among nine anecdotal reports of the association of TAD and PE [66-68, 82-87] there were four instances of coexisting DVT [66,68,83,87].

Neurological manifestations of PE other than stroke

The occurrence of seizures is an occasional manifestation of PE [64,65]. Syncope without concurrent signs and symptoms of venous thromboembolism is another atypical manifestation of PE. In one study, among 97 patients of mean age 77 with syncope as a manifestation of PE, there were 24 who had no manifestations of PE such as tachypnoea, tachycardia, hypotension or clinical signs or symptoms of DVT [88].

Delirium was attributable to PE in 5 patients aged 72-85, three of whom also had symptoms including chest pain and left calf swelling, acute dyspnoea, and sudden worsening dyspnoea, respectively. In the other two patients those symptoms were absent, and unexplained D-dimer increase was the only manifestation of PE. PaO₂ amounted to < 80 mmHg in four patients, but was documented as 83 mmHg in the fifth patient [89].

Pulmonary embolism-related PDE (Table 4)

In one study silent PE (identified by ventilation/perfusion imaging) had a documented prevalence of 37% among 151 patients with PDE [90]. However, in another study among 113 consecutive patients (mean age 62) with suspected cardiogenic embolic stroke and patent foramen ovale (PFO), CTPA identified

only 4 patients with PE [91]. An analysis of 12 anecdotal reports of PE-related PDE [92-105] reveals three patterns of clinical presentation (Table 4), namely, simultaneous occurrence of typical PE symptoms (or hypoxaemia) and symptoms of PDE, occurrence of PE symptoms followed by occurrence of stroke a day or so later, and occurrence of stroke without any documentation of breathlessness. In the latter category were four patients [102-105] in whom PDE-related stroke occurred in a PE patient who had reported neither breathlessness, chest pain or cough. Nevertheless, subsequent transthoracic echocardiography (TTE) revealed either right heart dilatation and elevation in pulmonary artery systolic pressure [103], or intracardiac thrombus [102, 104, 105], thereby raising the index of suspicion for PE. The utility of TTE in identifying PE in patients with PDE [102-105] has its counterpart in the utility of TTE for differentiating PE from suspected AMI [106]. In the latter case report a 32 year old man presented with anterior chest pain and dyspnoea, and he had ST segment elevation in V3-V6. TTE revealed right ventricular dilatation and dysfunction, and flattening of the interventricular septum signifying possible PE. The latter diagnosis was validated by CTPA [106]. TTE can also raise the index of suspicion for PDE in a patient with an acute exacerbation of asthma [107]. In the latter report a 69 year old woman with known asthma experienced an exacerbation of her symptoms which was accompanied by the occurrence of left upper limb pain. TTE revealed a tricuspid regurgitation peak gradient of 47 mm Hg which was indicative of pulmonary hypertension. Enhanced computed tomography revealed saddle PE. The left brachial artery was not delineated. Subsequent transoesophageal echocardiography revealed a PFO with right-to-left shunt during the Valsalva manoeuvre [107]. TTE can even identify the coexistence of PE and TAD, as in a 71 year old woman who presented with dyspnoea and angina. On examination she had DVT in one leg, and also had aortic regurgitation. TTE showed a thrombus in the right pulmonary artery, and stigmata of TAD comprising a dilated aortic root, an intimal flap with image suggestive of a double lumen, and moderate aortic regurgitation [87]. Even in the atypical presentation of PE with seizures TTE can raise the index of suspicion for PE by documenting stigmata consistent with PE [64,65].

Acute venous thromboembolism of atypical location

In one autopsy study the point of origin of PE was

Table 4: Pulmonary embolism-related paradoxical embolism.

First author and reference	Age	Sex	RR	SaO ₂ %	Typical PE symptoms or hypoxia	Simultaneous paradoxical embolism symptoms	Comments
Abusnina [92]	65	F	20	95	Y	Y	Right axillary artery embolism, DVT involving left femoral and left popliteal veins
Belvis [93]	36	F	NA	NA	Y	Y	Simultaneous dyspnoea and right hemiparesis
Bazan [94]	66	M	NA	NA	Y	Y	Simultaneous central cyanosis and bilateral ischaemic stroke
Liu [95]	57	M	NA	NA	Y	Y	Simultaneous dyspnoea and right cerebellar infarct
Vyas [96]	66	F	22	96	Y	Y	Simultaneous dyspnoea and stroke
Gansera [97]	32	F	NA	NA	Y	Y	Simultaneous dyspnoea and hemiplegia
Lapostolle [98]	53	F	NA	NA	Y	Y	Simultaneous hypoxaemia and hemiplegia
Lapostolle [98]	67	F	NA	85	Y	Y	Simultaneous hypoxaemia and hemiparesis
Lapostolle [98]	51	F	NA	88	Y	Y	Simultaneous dyspnoea and hemiplegia
Lapostolle [98]	56	M	NA	NA	Y	Y	Oxygen saturation 95%, breathing 3L oxygen/min, hemiplegia
Facciorusso [99]	73	F	NA		Y	N	Dyspnoea followed by stroke 4 weeks later
Almaghraby [100]	61	M	24	NA	Y	N	Dyspnoea followed by stroke 2 days later. Deep vein thrombosis in both lower limbs
Mirijello [101]	58	M	NA	94	Y	N	Pleuritic pain followed by stroke the following day
First author and reference	Age	Sex	RR	SaO ₂ %	Typical PE symptoms or hypoxia	Simultaneous paradoxical embolism symptoms	Comments
Kumar [102]	32	M	NA	NA	N	N	Stroke and echocardiogram showing thrombus in foramen ovale, thrombus in main pulmonary artery. DVT right common iliac vein
Cameron [103]	53	M	31	NA	N	N	Hemiparesis and echocardiogram showing right ventricular dilatation and pulmonary hypertension. CTPA showed PE
Dada [104]	55	M	NA	NA	N	N	Hemiparesis and echocardiogram showing patent foramen ovale, right atrial embolus and pulmonary embolus
Miriyala [105]	72	M	NA	NA	N	N	Hemiparesis and echocardiogram showing thrombus in right atrium and foramen ovale and pulmonary artery. Bilateral lower limb DVT

Key: F: Female; M: Male; RR: Respiratory Rate; SaO₂: Oxygen saturation on room air; N: No; Y: Yes; NA: Not available

identified in 102 out of two hundred cases of proven PE. In 36.9% of cases point of origin included periureteric plexus, superior vena cava, and right atrium [108]. A systematic review of twenty nine publications revealed that DVT of the upper extremity constituted 4% to 10% of all DVT during the period January 1980 to May 2016 [109]. Internal jugular vein thrombosis, exemplified by Lemierre's syndrome is another risk factor for PE [110].

Exceptionally, jugular venous thrombosis can be complicated by the occurrence of paradoxical embolism, as was the case in a 23 year old woman who presented with chest pain and breathlessness, in the context of previous documentation of right internal jugular vein thrombosis. In addition to CTPA-validated PE she had angiographic evidence of emboli to the arm and leg [111].

Pulmonary thromboembolism with normal serum D-dimer levels

Although an elevated D-dimer level is a useful confirmatory test for PE, a prospective study of 1,632 subjects in the age range 20-100 identified 8 patients aged 28-71 with CTPA-validated PE in whom D-dimer levels did not exceed 500 mcg/L [112].

An age-adjusted D-dimer evaluation (age x 10 mcg/L with

a lower limit of 500 mcg/L) does not necessarily mitigate the risk of misdiagnosis of PE. A missed diagnosis of PE was documented in a 75 year old man with a normal age-adjusted D-dimer level. He had presented with recent-onset progressive dyspnoea, wheezing, and cough. The oxygen saturation whilst breathing room air was 93%. Atypically, his Wells score was zero, and his age-adjusted D-dimer was 600 mcg/L (normal level for age-adjusted D-dimer). In spite of atypical clinical presentation (ie Wells score of zero) and atypically normal age-adjusted D-dimer, CTPA showed several segmental emboli in both upper and lower parts of the right lung [113].

Summary of the prevalence of some of the atypical manifestations

Evaluation of anecdotal reports of atypical manifestations of PE is fraught with limitations attributable to publication bias. Within the constraints imposed by those limitations the following generalisations are possible:-

(i) Presentation of PE with STEMI-like ST segment elevation is a rare entity, generating only 34 case reports in a recent systematic review. Nevertheless, it emerged that PE-related ST segment elevation occurs predominantly in the anteroseptal distribution [13].

(ii) Presentation with gradual onset dyspnoea is prevalent in approximately 3% of patients with PE [30,114].



(iii) Orthopnoea is rare, occurring in approximately in 1% of PE patients [30,114]

(iv) Oxygen saturation of < 95% (while breathing room air) generates an Odds Ratio of 3.3 in favour of the diagnosis of PE among patients with suspected PE [3].

(v) Syncope is prevalent in approximately 22%-26% of PE patients [30],[114].

(vi) PE-related paradoxical embolism is rare, and stroke is its commonest manifestation. Among patients with embolic stroke associated with patent foramen ovale, the prevalence of PE may only be 3.5% [9].

(vii) Deep vein thrombosis of atypical location is a rare risk factor for PE. Upper limb DVT is a specific example, prevalent in 4%-10% of all patients with DVT [109]

(viii) Approximately 0.5% of PE patients have D-dimer levels amounting to < 500 mcg/L (ie the normal reference range) [112].

Conclusion

Atypical manifestations of PE may occur in patients who already have at least one other symptom or sign which has been enumerated in a CDR or in PERC. If an atypical symptom dominates the clinical picture the risk is that a diagnosis other than PE might seem more likely. The index of suspicion for PE is even more likely to be diminished if atypical signs and symptoms are the sole presenting features of PE, thereby making an alternative diagnosis even more likely than PE. The latter scenario is exemplified by initial sole presentation of PE as abdominal pain, hoarseness, hiccups, seizures, syncope, or paradoxical embolism, respectively, without concurrent dyspnoea, and also without concurrent chest pain. Attention to atypical symptoms and signs of PE, and awareness of the entire range of manifestations of PE can improve the level of pulmonary embolism diagnosis.

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