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Pulmonary tumor thrombotic microangiopathy: a systematic review

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Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is a fatal disease process in which pulmonary hypertension (PH) develops in the setting of malignancy. The purpose of this study is to present a detailed analysis of cases of PTTM reported in literature in the hopes of achieving more ante-mortem diagnoses. We conducted a systematic review of currently published and available cases of PTTM by searching the term “pulmonary tumor thrombotic microangiopathy” on the Pubmed.gov database. Seventy-nine publications were included consisting of 160 unique cases of PTTM. The most commonly reported malignancy was gastric adenocarcinoma (94 cases, 59%). Cough and dyspnea were reported in 61 (85%) and 102 (94%) cases, respectively. Hypoxemia was reported in 96 cases (95%). Elevation in D-dimer was noted in 36 cases (95%), presence of anemia in 32 cases (84%), and thrombocytopenia in 30 cases (77%). Common findings on chest computed tomography (CT) included ground-glass opacities (GGO) in 28 cases (82%) and nodules in 24 cases (86%). PH on echocardiography was noted in 59 cases (89%) with an average right ventricular systolic pressure of 71 mmHg. Common features of PTTM that are reported across the published literature include presence of dyspnea and cough, hypoxemia, with abnormal CT findings of GGO, nodules, and mediastinal/hilar lymphadenopathy, and PH. PTTM is a universally fatal disease process and this analysis provides a detailed examination of all the available published data that may help clinicians establish an earlier diagnosis of PTTM.

Keywords

pulmonary hypertension, cancer, embolism, dyspnea

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a disease process in which tumor cells embolize to the pulmonary vasculature; there is activation of the coagulation cascade, formation of fibrin clots, and fibrocellular proliferation of the intimal layer of blood vessel walls. Elevated pulmonary artery pressures (PAP) are observed and death results from right heart failure. PTTM is most commonly associated with gastric adenocarcinoma but has been described in numerous other carcinomas.¹ In recent years, PTTM has been reported with increasing frequency. The pathophysiology is not completely understood and patient outcomes remain poor with rapid decline in clinical condition often occurring within weeks of symptom onset.

The purpose of this systematic review is to help achieve improved rates of ante-mortem diagnosis of PTTM by presenting a comprehensive analysis of patient symptomatology, clinical examination findings, laboratory abnormalities, radiographic features, pulmonary hypertension (PH), and histologic observations reported across the published literature. We also review attempted treatments and clinical outcome and discuss future directions for research.

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Methods

We conducted a systematic review of currently published and available cases of PTTM. First, we queried the term “pulmonary tumor thrombotic microangiopathy” on the Pubmed.gov database in June of 2018 and received 284 search results. After applying filters for publications in the English language and those pertaining to humans, 183 items remained. The University of California library system was used to access and screen each publication for inclusion for the systematic review. Articles that pertained to PTTM and those that presented original data on reported cases of PTTM were included. Review articles, articles not in the English language, and inaccessible articles were excluded. In total, 120 articles were eliminated for the following reasons: the publication was not about PTTM ($n=102$); the publication was a reply or comment regarding another publication ($n=8$); the article could not be accessed ($n=5$); and the publication was a review article ($n=4$). One publication was an interactive case based on a publication that was included ($n=1$). Sixteen publications were included which were missed by the queried term but were found by other means (prior knowledge of the publications or as references in included publications).

A total of 79 publications were included in the systematic review; this included 66 case reports and 13 case series.^{1-37,45-92} For each patient described in the publications, the following information was collected, if available: age; gender; history of tobacco smoking or alcohol consumption; presence or absence of commonly reported symptoms (cough, dyspnea, hemoptysis, fatigue, weight loss, abdominal pain, night sweats, and syncope); signs of PH and/or right heart failure on examination (jugular venous distension, loud P2 component of S2 heart sound, holosystolic murmur at left sternal border, right ventricular heave, pulsatile liver on palpation, etc.); presence or absence of hypoxemia (on pulse oximetry or arterial blood gas analysis); laboratory abnormalities (elevation of D-dimer and lactate dehydrogenase, anemia, thrombocytopenia, or diagnosis of disseminated intravascular coagulation [DIC]); abnormal chest radiography; presence or absence of abnormalities on chest computed tomography (CT) (nodules, septal thickening, ground glass opacities [GGO], tree-in-bud opacities, mediastinal or hilar lymphadenopathy, pleural effusions, and pulmonary embolism [PE]); elevated right ventricular (RV) pressure or pulmonary artery pressures (PAP) by two-dimensional transthoracic echocardiography and/or right heart catheterization (RHC); presence of serum tumor markers or immunohistochemical staining of fixed tissue specimen (vascular endothelial growth factor [VEGF]; platelet-derived growth factor [PDGF]; tissue factor [TF]; 5-HT2A, serotonin receptor; and osteopontin [OPN]); presence of characteristic histologic findings (tumor emboli, luminal fibrin deposition, fibrocellular intimal hyperplasia); identity of the causative primary malignancy; and attempted treatment by class of medication. Information

pertaining to the patient’s clinical course was collected, including whether PTTM was diagnosed ante-mortem or post-mortem; the duration of time from the diagnosis of the primary malignancy to the development of PTTM; and the time to death after the onset of symptoms. Clinical findings were logged in a binary fashion (present/absent, yes/no, etc.). Time was rounded to the nearest half-week or one-tenth of a year and pulmonary pressures to the nearest whole number. The frequency of a particular finding was calculated based only on “reporting” cases. For example, 27 cases reported a diagnosis of DIC accounting for 48% of reporting cases because 29 cases (52%) reported an absence of DIC. A significant number of publications did not include the presence or absence of certain findings of PTTM, and thus, were considered “non-reporting.” The number of “non-reporting” cases is noted when applicable. Many of the “non-reporting” cases were part of larger retrospective autopsy case series, which did not include information such as presenting symptoms or physical examination findings. Radiographic features of PTTM were compared between the various primary malignancies and the difference in proportions was calculated by the N-1 Chi squared test. PTTM is compared to its clinical mimic, chronic thromboembolic pulmonary hypertension (CTEPH), in the “Discussion” section. We could not compute any objective risk of bias though publication bias likely exists.

Results

Seventy-nine publications consisting of 160 patients with PTTM were studied (Table 1). There were 89 men (56%) and 71 women (44%). The average patient age was 56 years (median age = 58 years, age range = 11–89 years). Twelve cases had a history of smoking while nine cases did not (139 cases non-reporting). Gastric adenocarcinoma was diagnosed in 94 cases (59%), breast cancer in 16 cases (10%), lung cancer in 10 cases (6.3%), urothelial carcinoma in six cases (3.8%), and ovarian carcinoma in four cases (2.5%). The diagnosis of the causative primary malignancy was made ante-mortem in 57 cases (65%, 72 non-reporting) and post-mortem in 31 cases (35%). In those cases where primary malignancy was diagnosed ante-mortem, the average length of time after the diagnosis of the primary malignancy and before presentation with PTTM is known in 21 cases and is, on average, 3.5 years (median = 2 years, range = 0.1–12 years).

Ante-mortem diagnosis of PTTM, in which lung tissue was available after biopsy, was made in 15 cases (9.4%). On the other hand, PTTM was diagnosed clinically, without lung biopsy, in seven cases (4.4%). Most cases of PTTM ($n=127$; 79%) were diagnosed at the post-mortem examination. The time from onset of symptoms to death was calculated in weeks and found to be an average of 9.5 weeks (median = 3 weeks; range = <0.5–88 weeks; 64 non-reporting cases).

Dyspnea was reported in 102 cases (94%; 52 non-reporting) and cough in 61 cases (85%; 88 non-reporting).

Table 1. Search results, inclusion, and exclusion.

Total search results	284
Filters for English language and human studies	183
Included	79
- Case reports	66
- Case series	13
Excluded	
- Not about PTTM	102
- Reply to another article	8
- No access	5
- Review article	4
- Duplicate	1
Articles included but not found through PubMed	16

Hypoxemia was reported in 96 cases (95%; 59 non-reporting). Table 2 shows the other presenting symptoms of PTTM.

Abnormal laboratory studies included: elevation in D-dimer in 36 cases (95%; 122 non-reporting); presence of anemia in 32 cases (84%; 122 non-reporting); and thrombocytopenia in 30 cases (77%; 121 non-reporting). DIC was diagnosed in 27 cases (48%; 104 non-reporting).

The chest radiograph was reported to be abnormal in 39 cases (70%; 104 non-reporting). Notable findings on the chest CT included: GGO in 28 cases (82%; 126 non-reporting); nodules in 24 cases (86%; 132 non-reporting); mediastinal and/or hilar lymphadenopathy in 19 cases (91%; 139 non-reporting); and septal thickening in 17 cases (81%; 139 non-reporting).

In 68 cases, chest CT noted the presence of at least one of the aforementioned findings. Table 3 lists the abnormal findings on chest CT for each of the three most commonly reported primary malignancies. In gastric cancer, the most common finding on chest CT was mediastinal/hilar lymphadenopathy (16/19, 84%). Table 4 outlines the differences in CT chest features between gastric cancer and breast, lung, and all other non-gastric cancers. There is a statistically significant difference in the frequency with which septal thickening is reported between gastric cancer and breast cancer ($P=0.02$, 95% confidence interval [CI]=6.08–86.6) as well as gastric cancer and all non-gastric cancers ($P=0.05$, 95% CI=0.164–66.0). Sensitivity and specificity of each CT finding that would indicate PTTM from gastric cancer is noted in Table 5. Septal thickening, nodules, and mediastinal/hilar lymphadenopathy have a sensitivity of 92%, 93%, and 100% and specificity of 38%, 23%, and 40%, respectively, for the diagnosis of PTTM due to gastric cancer.

PH, as assessed by transthoracic echocardiography (TTE), was reported in 59 cases (89%; 94 non-reporting). The average right ventricular systolic pressure (RVSP) or pulmonary artery systolic pressure (PASP) on TTE was 71 mmHg (median = 68 mmHg, range = 34–140 mmHg). RHC data are available from 22 cases. The average values

Table 2. Demographics, presenting symptoms, and primary malignancy.

	n (%)
Age, years (mean)	56
Gender	
Men	89 (56)
Women	71 (44)
Risk factors for malignancy	
Tobacco smoking	9 (57)
Alcohol use	2 (50)
Symptoms	
Cough	61 (85)
Dyspnea	102 (94)
Hemoptysis	9 (23)
Fatigue	11 (73)
Weight loss	10 (59)
Abdominal pain	11 (86)
Night sweats	5 (42)
Syncope	6 (43)
Hypoxemia	96 (95)
Primary malignancy	
Gastric	94 (59)
Breast	16 (10)
Lung	10 (6)
Urothelial	6 (4)
Unknown	4 (3)
Ovarian	4 (3)
Pancreatic	3 (2)
Esophageal	3 (2)
Prostate	2 (1)
Colon	2 (1)
Gallbladder	2 (1)
Hepatocellular, dual parotid gland/salivary duct, dual hepatocellular/cholangiocarcinoma, dual gastric/duodenal, cholangiocarcinoma, sphenoid sinus, gastroesophageal junction, extramammary Paget's disease, salivary duct, primary myelodysplastic syndrome, desmoplastic small round cell tumor, angiosarcoma, kidney malignant rhabdoid tumor, renal papillary carcinoma	1 (1)

Percentages are calculated based on all the "reporting" cases. See references 1-37 and 46-92 for case reports and series of PTTM. n, number of cases.

(median, range) are as follows: mean pulmonary arterial pressure (mPAP) of 48 mmHg (median = 48 mmHg, range = 34–70 mmHg); pulmonary vascular resistance (PVR) of 13 Wood units (median = 12 WU, range = 4–23 WU); pulmonary capillary wedge pressure (PCWP) of 15 mmHg (median = 12 mmHg, range = 6–35 mmHg); cardiac output of 3.8 L/min (median = 4 L/min, range = 2–6.5 L/min); and cardiac index of 2.0 L/min/m²

Table 3. Common chest CT features of PTTM.

Malignancy	GGO (%)	Nodules (%)	Tree-in-bud (%)	Septal thickening (%)	Mediastinal/hilar adenopathy (%)	Infiltrates/consolidations (%)	Pleural effusion (%)
Gastric	10 (36)	14 (58)	6 (55)	12 (71)	16 (84)	7 (47)	5 (38)
Breast	4 (14)	4 (17)	0 (0)	1 (6)	2 (11)	2 (13)	1 (8)
Lung	2 (7)	1 (4)	2 (18)	2 (12)	1 (5)	2 (13)	2 (15)
Total non-gastric	18 (64)	10 (42)	5 (45)	5 (29)	3 (16)	8 (53)	8 (62)
Overall*	28	24	11	17	19	15	13

This table shows radiographic findings and the relative proportions (in parenthesis) of each finding in the three most common primary malignancies reported in patients with PTTM as well as the total non-gastric cases.

*Overall includes number of cases reporting a particular radiographic finding.

Table 4. Comparison of proportions of each radiographic finding between commonly reported malignancies.

Malignancy	Comparison	GGO	Nodules	Tree-in-bud	Septal thickening	Mediastinal/hilar adenopathy	Infiltrates/consolidations	Pleural effusion
Gastric	Breast	N/A	0.12 (−6.41–63.9)	N/A	0.02 (6.08–86.6)	N/A	0.79 (−42.5–46.5)	0.52 (−32.0–59.6)
Gastric	Lung	0.75 (−28.5–57.0)	0.09 (−3.73–83.9)	1.000 (−47.4–47.4)	0.25 (−12.0–71.7)	N/A	0.79 (−42.5–46.5)	N/A
Gastric	Non-gastric	0.10 (−4.49–45.6)	0.24 (−11.6–43.8)	N/A	0.05 (0.164–66.0)	N/A	0.28 (−16.3–52.0)	0.27 (−15.8–56.7)

This table illustrates statistical significance of CT findings between different types of malignancies in cases of PTTM. Septal thickening is a radiographic feature that is statistically more common in gastric cancer than in breast cancer or all non-gastric cancer cases. *P* values are listed with 95% CIs in parentheses.

Comparison of proportions online calculator was used for this statistical analysis (https://www.medcalc.org/calc/comparison_of_proportions.php)

N/A, comparison of proportions cannot be done in cases if proportion is either 0% or 100%.

Table 5. Sensitivity and specificity of radiographic findings for gastric cancer versus non-gastric cancers causing PTTM.

	GGO	Nodules	Tree-in-bud	Septal thickening	Mediastinal/hilar adenopathy	Infiltrates/consolidations	Pleural effusion
Sensitivity	75% (10/15)	93% (14/15)	50% (6/12)	92% (12/13)	100% (16/16)	58% (7/12)	56% (5/9)
Specificity	5% (1/19)	23% (3/13)	29% (2/7)	38% (3/8)	40% (2/5)	20% (2/10)	20% (2/10)

This table shows the sensitivity and specificity of each radiographic finding for identification of gastric cancer as the primary malignancy causing PTTM.

GGO, ground-glass opacities.

(median = 2.0 L/min/m², range = 1.3–3.2 L/min/m²). In total, three patients had a PCWP > 15 mmHg, while the rest had pre-capillary PH.

The treatments that have been attempted for PTTM are in the following classes of medications: advanced PH therapy (phosphodiesterase inhibitor, endothelin-receptor antagonist, prostacyclin analogue, and inhaled nitric oxide); anti-neoplastic agents; anticoagulants; diuretics; and corticosteroids (Table 6). Fourteen patients underwent treatment with advanced PH therapy while 17 patients received anti-neoplastic agents. Of the 14 that received advanced PH therapy, 11 (79%) had undergone a RHC. Of those, some treatment regimens may have extended the life of patients beyond what was expected, on the order of months (Table 7).

The serum tumor markers and/or immunohistochemical staining of tissue associated with PTTM and their frequencies of positive results were as follows: VEGF in 63 cases (96%; 94 non-reporting); TF in 55 cases (100%; 106 non-reporting); PDGF in 32 (74%; 117 non-reporting); and OPN in 30 cases (64%; 113 non-reporting). Lung tissue, obtained either by biopsy or at autopsy, revealed tumor emboli and thrombus formation in association with fibrocellular intimal proliferation in 117 cases (100.0%; 43 non-reporting).

Discussion

PTTM is a difficult diagnosis to establish and most cases are diagnosed post-mortem. Based on unselected autopsy case

Table 6. Medications used previous in PTTM.

Medication class	Medication name	Cases (n)
Advanced PH therapy	Sildenafil	14
	Tadalafil	
	Ambrisentan	
	Bosentan	
	Epoprostanol	
Anti-neoplastic drugs	Imatinib	17
	TS-I chemo	
	Irinotecan	
	S-I (tegafur, gemaricil, oteracil)	
	5-Fluorouracil	
	Cisplatin	
	Nedaplatin	
	Capecitabine	
	Oxaliplatin	
	Epirubicin	
Diuretics	Furosemide	6
	Spironolactone	
Corticosteroids	Dexamethasone	16
	Prednisone	
Anticoagulation	Warfarin	15

series of patients with carcinoma, characteristic histologic features of PTTM were seen in 1.4% and 3.3% of cases.^{1,2} Among autopsy cases of gastric cancer alone, features of PTTM were seen in 16.7% of cases.³ The purpose of this systematic review is to present an analysis of patient symptomatology, clinical examination findings, laboratory abnormalities, radiographic features, PH, and histologic observations reported across the published literature. The limitation of this systematic review includes publication bias as many cases of PTTM may go unpublished, which may significantly affect the results including reported frequencies of findings presented herein.

Symptoms and physical examination

The symptoms associated with PTTM can easily be attributed to benign etiologies, potentially leading clinicians away from establishing an accurate diagnosis. Cough in PTTM is generally reported as dry, can persist throughout the day, and gets progressively worse.⁴⁻⁶ Cough can present as early as a year before presentation or late in the course of the disease.⁷⁻¹² Absence of cough has also been noted.^{13,14} The exact mechanism of cough is not completely understood, but in two cases of PTTM, the initiation of chemotherapy alleviated it, suggesting a mechanism that involves tumor infiltration of airway mucosa and stimulation of cough receptors.^{6,15,16}

Dyspnea is frequently noted to be progressive and insidious. Exertional dyspnea generally progressed to resting dyspnea.^{5,7,17} Dyspnea may be subacute, with onset months before presentation, or may be rapidly progressive, with

one patient being able to run a half-marathon two months before presentation but who could not climb a flight of stairs at presentation.^{13,14} Dyspnea on exertion is sometimes present along with the symptoms of orthopnea and paroxysmal nocturnal dyspnea and examination findings of jugular venous distension and lower extremity edema.¹⁸ Cough can be followed by progressively worsening dyspnea or it can start after the onset of dyspnea.^{7,18} The pathophysiology of dyspnea, which is sometimes noted to occur with malaise, may be due to PH resulting in increased RV afterload, reduced RV cardiac output, and hypoxemia. Exaggerated pulsus paradoxus from a dilated RV and reduction in left ventricular output may also be a contributing factor. Dyspnea as a result of airflow obstruction, especially during episodes of cough, is also a possible mechanism.¹⁶ Although cough and dyspnea are the most commonly reported symptoms, other symptoms may provide a clue as to the origin of the primary malignancy. While gastric cancer can present with a paucity of symptoms, symptoms such as abdominal pain and weight loss may be due to gastric adenocarcinoma, the most commonly reported malignancy associated with PTTM.

Hypoxemia

Patients with PTTM will nearly invariably develop hypoxemia. Most, but not all patients, present to the hospital with some degree of hypoxemia. Patients who presented with significant hypoxemia requiring supplemental oxygen survived only days or a few weeks after presentation.^{14,19} Hypoxemia was noted upon exertion during a 6-min walk test in one case, which worsened over the course of a few days to hypoxemia at rest.⁷ Progression can be even more rapid: one patient with normal oxygen saturation of 96% at presentation developed hypoxemia within one day and subsequent cardiac arrest within three days of presentation.⁹ There was presence of jugular venous distension, loud P2 component of the S2 heart sound, gallop S3 heart sound, and/or RV heave in 10 cases implying heart failure and PH. Reduction in RV cardiac output due to severe PH and volume/pressure overload, reduction in LV cardiac output, increased shunting, tumor infiltration of the alveolar lining, and impairment of gas diffusion across the capillary membrane may be the mechanisms of hypoxemia. The degree of hypoxemia is likely related to the extent of metastatic disease affecting gas exchange, the degree of shunting, and the severity of PH affecting RV cardiac output. Treatment of both the malignancy as well as the underlying vasculopathy may help prevent acute decompensation of the RV and help prevent worsening hypoxemia and respiratory failure.

Laboratory abnormalities

The most common abnormalities in laboratory analysis include elevation of D-dimer, presence of anemia, development of thrombocytopenia, and elevation of LDH. It has

Table 7. Treatment and outcomes.

Publication (reference)	mPAP (S/D) before therapy (mmHg)	mPAP (S/D) after therapy (mmHg)	CI before therapy (L/min/m ²)	CI after therapy (L/min/m ²)	Primary malignancy	Therapy	Survival (months)
<i>Publications showing improvement in PH and survival</i>							
Fukada et al. ³³	60 (93/39)	50 (87/30)	1.63	2.83	Breast adenocarcinoma	Imatinib (200 mg/d*), tadalafil 40 mg	1-3/4
Higo et al. ¹⁵	48 (77/31)	35 (69/17)	1.82	4.64	Colon adenocarcinoma	Imatinib (50 mg/day [†]), bevacizumab (5 mg/kg), S-I [‡] (100 mg/day)	12
Kubota et al. ³²	46 (70/31)	22 (35/12)	NA	NA	Gastric adenocarcinoma	Imatinib (200 mg/d), bosentan (62.5 mg), tadalafil (40 mg), TS-I, oxaliplatin	7
Ogawa et al. ^{31,***}	~ 47	~ 23	~ 2	~ 4	Gastric and duodenal adenocarcinomas	Bosentan, epoprostanol (3.8 ng/kg/min) catecholamines, imatinib (100 mg/d), TS-I	10
Minatsuki et al. ³⁰	48	13	2.69	2.71	Gastric adenocarcinoma	Imatinib (200 mg/d), tadalafil (20 mg), sildenafil (60 mg), ambrisentan (10 mg)	13
<i>Publications showing improved survival without information regarding PH</i>							
Miyano et al. ¹⁰	NA	NA	NA	NA	Gastric adenocarcinoma	S-I, dexamethasone, warfarin, aspirin	7 ^{††}
Kayatani et al. ⁶	NA	NA	NA	NA	Adenocarcinoma of unknown origin	S-I, cisplatin, S-I, gemcitabine 10 months later with recurrence of symptoms	15
<i>Publications showing no improvement in PH with associated survival</i>							
Purga et al. ³⁴	37 (64/22)	38 (70/22)	1.7	2.0	Ovarian adenocarcinoma	iNO, dobutamine, dopamine, vasopressin, treprostinil	1
Endicott-Yazdani et al. ⁴⁵	37 (70/30)	NA (worsening PH but pressures not reported)	NA	NA	Gastric adenocarcinoma	Epoprostanol	2.5

*Administered as part of a clinical trial with approval from the institutional review board. Imatinib dose was increased to 400 mg after reduction in PAP.

[†]Imatinib started at 50 mg/day and gradually increased to 200 mg/day.

[‡]S-I consists of tegafur, gimeracil, and oteracil potassium.

^{***}Measurements are estimates because they were extrapolated from a graph and values of mPAP and CI were not explicitly stated

^{††}PH was not present in this case on echocardiography but it is unclear when during the patient's clinical course the echocardiography was performed. The patient was followed for seven months, at which time she was doing well but no further follow-up was published.

CI, cardiac index; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; NA, not available; S/D, systolic/diastolic; TS-I, titanium silicate I.

been hypothesized that tumor cell embolization to pulmonary arterioles induces the activation of coagulation, platelet aggregation, and release of various cytokines derived from platelets, tumor cells, and endothelial cells including PDGF and VEGF.^{1,20}

Anemia and elevation in the LDH may be a result of shearing of erythrocytes passing through the pulmonary circulation.¹ Thrombocytopenia may be due to increased consumption from DIC, increased sequestration, reduced production due to tumor cell infiltration of the bone marrow, or an unknown mechanism related to acute critical illness. Elevated D-dimer is most likely due to the activation of coagulation cascade, aggregation of platelets, and subsequent breakdown of fibrinogen into fibrin degradation products.²⁰ The aforementioned laboratory abnormalities develop over time and thus it is possible that a patient with underlying PTTM may not have any laboratory abnormalities or may present with a singular salient abnormality such as an anemia or elevation in LDH or D-dimer.²¹ A significant number of patients (27 cases; 48%) noted the development of DIC. Carcinomas are known to be a provoking factor for the development of DIC.²²

The time course of the development of the aforementioned laboratory abnormalities potentially informs the clinician of the aggressiveness of the underlying malignancy as well as the severity of the vasculopathy, including occlusion of vasculature by tumor emboli, damage to endothelium, activation of the coagulation system, and formation of fibrin strands causing hemolysis.¹

Radiographic features

The chest radiograph was reported abnormal in 70% of the cases. Specific findings on the chest radiograph were not recorded due to the significant variation in the description of the abnormalities. In addition, chest radiographic findings were not reported in 104 cases. It is reasonable to say that the main purpose of the chest radiograph is to expedite further testing including a chest CT and echocardiogram. In circumstances where the radiograph is normal, a high index of clinical suspicion would be required to prompt additional studies.²³ In the case of normal chest radiography, non-resolving or progressive symptoms and hypoxemia should prompt an expedited work-up.

The chest CT commonly revealed features of GGO, nodules, septal thickening, mediastinal/hilar lymphadenopathy, and consolidation (Tables 3–5). The ground-glass opacification may reflect tumor infiltration of alveolar septae.²⁴ Nodules are generally seen in a centrilobular distribution and are most likely to result from hematogenous spread of malignancy through pulmonary arterioles.¹⁹ The histologic correlate of septal thickening is understood to be engorgement of lymphatic channels.¹⁹ While some studies have previously reported pulmonary venular involvement, the radiographic correlates specific to pulmonary venules are unknown.^{19,25} Finally, mediastinal and hilar

lymphadenopathy probably results from drainage of tumor cells via interlobular lymphatic channels or drainage via the thoracic duct in gastric cancer.

The metastatic spread of the primary malignancy, whether by hematogenous or lymphatic means, likely influences the radiographic features seen in PTTM. There is considerable overlap in the radiographic features and source of the primary cancer. However, we noted that there was a significant difference in the proportion of patients with septal thickening who also harbored gastric cancer versus breast cancer and versus all non-gastric cancer. These findings should be interpreted with caution as they are based on a small number of patients. As more cases are reported, the presence and absence of commonly reported CT findings should be published to help improve the distinction between radiographic features in PTTM due to different primary malignancies.

We also calculated the sensitivity and specificity of each CT feature for gastric cancer as the underlying primary malignancy causing PTTM given the larger number of reported cases in the literature. Septal thickening, nodules, and mediastinal/hilar lymphadenopathy have high sensitivity but low specificity. Again, the results should be interpreted with caution because of the considerable publication bias which likely skews the data towards the presence of certain CT findings rather than their absence. Thus, both sensitivity and specificity could be significantly higher or lower than what is reported here.

The use of 18-fluoro-deoxyglucose (FDG) positron emission tomography (PET) and ventilation-perfusion (V/Q) scans for the diagnosis of PTTM has been limited.^{19,20} One case reported seeing evidence of FDG uptake suggestive of metastatic cancer though the primary malignancy could not be identified (at autopsy, the primary malignancy was discovered to be in the stomach).²⁶ One case reported wedge-shaped defects on perfusion scanning of the lung in a patient with PTTM.²⁷

Pulmonary hypertension

PH due to PTTM most likely occurs as a result of luminal occlusion by tumor cells, fibrin deposition, and fibrocellular intimal hyperplasia, thus increasing PVR. The degree of stenosis of vessels and how widespread the vasculopathy is throughout the lungs may influence the severity of the PH.²⁸ In the World Health Organization (WHO) classification system, PTTM fits under the miscellaneous Group 5 PH category.^{20,29} At the time of presentation to the hospital, 10 cases noted an abnormal physical examination with signs of volume overload including jugular venous distension and lower extremity edema as well as fixed splitting of S2 heart sound with a loud P2 component, indicating PH. An echocardiogram is indicated as soon as possible to identify PH and the degree of RV dysfunction. In our prior analysis of seven cases of PTTM, the echocardiogram was obtained an average of nine days after the initial clinical

presentation (range = 1–28 days, median = 5 days). The two patients with the greatest delays, 17 and 28 days, had presented in the outpatient setting (unpublished data).

The rapidity of progression is most probably related to the ability of the right ventricle to compensate for the pressure and/or volume overload. In one patient whose dyspnea began two months before presentation, the echocardiogram showed a dilated right ventricle but no compensatory hypertrophy and with a PASP of 75 mmHg.¹⁴ In many cases, a RHC is not done due to rapid clinical decline.

In this analysis, there were 22 patients that underwent a RHC; among them, 11 were started on advanced PH medications and five on anti-neoplastic medications. We noted five cases in which a RHC documented improvement in the mPAP (Table 7). In four of those cases, the mean survival was 10.5 months (median = 11 months, range = 7–13 months). These findings do raise the question of whether early initiation of treatment to ameliorate the right ventricular pressure and volume overload could increase survival.

RHC may be useful in several contexts. First, it allows for an assessment of hemodynamics, especially when physical examination or echocardiography is ambiguous. Second, it may guide initiation of advanced PH therapy (e.g. endothelin receptor antagonists, prostacyclin analogues), diuresis, inotropic support, and even anti-neoplastic drugs.^{30,31} In five particular cases (Table 7) of PTTM where imatinib was administered, there was an improvement in the mPAP in each case and improvement in survival in four out of five patients compared to what is normally expected with PTTM.^{15,30,32,33} In one of these cases, anti-neoplastic drugs imatinib and bevacizumab were administered without advanced PH medications and yet the patient survived for 12 months.¹⁵ Another patient suffering from ovarian cancer received advanced PH therapy with inhaled nitric oxide and intravenous treprostinil without anti-neoplastic agents and her condition deteriorated over one month.³⁴ This raises the question that anti-neoplastic agents are potentially efficacious and adjunct PH therapy may be important. Prospective trials will be needed to help clarify treatment options in PTTM. Imatinib specifically is discussed later.

Finally, RHC may allow for sampling of blood from the pulmonary artery, which in some cases reveals the presence of tumor cells, allowing for a diagnosis of the primary malignancy and/or tumor emboli.³⁵ RHC need not always be pursued, especially if there is sufficient evidence, based on the overall clinical picture, to suspect a diagnosis of PTTM.

Lung histology, immunohistochemistry, and serum tumor markers

In the literature, lung histology has consistently revealed tumor cells within the lumen of pulmonary pre-capillary vessels, with surrounding fibrin deposition along with fibrocellular intimal hyperplasia. One publication studied the degree of stenosis of pulmonary pre-capillary vessels among six autopsy cases of PTTM. There was an inverse

relationship between vessel diameter and the degree of stenosis. PH was assessed only in two cases and there appeared to be a correlation between PH and the degree of stenosis as well as how diffuse the vasculopathy was throughout the lung.²⁸ Pulmonary venular and lymphatic involvement have also been documented in the literature.^{1,19,25}

Immunohistochemical staining revealed tumor cells staining positively for PDGF, VEGF, TF, and OPN. The pathophysiology of PTTM involves a complex interplay between tumor cells, endothelial cells, smooth muscle cells, inflammatory cells, mediators of inflammation (PDGF and VEGF released by tumor cells) and tissue repair (OPN released by tumor cells, macrophages, and fibrointimal cells), and activators of the coagulation system (TF released by tumor cells and endothelial cells).^{20,35,36} Upon the embolization of tumor cells into pulmonary vasculature, endothelial injury releases TF which initiates the coagulation cascade and formation of fibrin clots. Platelet aggregation occurs and platelets release cytokines and chemokines, including PDGF, which attract macrophages to the area of inflammation.²⁰ Tumor cells also release PDGF and VEGF which stimulates fibrocellular intimal thickening and angiogenesis.²⁰ PDGF upregulates the production of OPN, a glycoprotein, that is released at sites of endothelial damage and inflammation, and may be involved in vascular remodeling.³⁵ VEGF promotes the cleavage of OPN, creating fragments that act as a chemoattractant for smooth muscle cells, suggesting a role in smooth muscle cell proliferation and angiogenesis.^{35,37,38}

PDGF and VEGF levels have been measured in the serum. Their role in clinical care will likely not be in the diagnosis of PTTM but rather in assessing response to treatment.^{30,31} One case report demonstrated a decrease in the PDGF level from about 3000 pg/mL to < 500 pg/mL within 30 days after the initiation of imatinib.³¹ In another case report, a decrease in VEGF levels from 240 pg/mL to 15.6 pg/mL was seen after treatment with dexamethasone, warfarin, aspirin, and S-1 chemotherapy.¹⁰

Clinical mimic

The two diseases, CTEPH and PTTM, share some similarities but there are significant differences. In both entities, a high index of clinical suspicion is required to make the diagnosis. Symptomatically, both conditions may present with dyspnea. However, cough is a common symptom in PTTM but is less common in CTEPH.⁴⁰ CTEPH generally progresses over longer periods of time while PTTM progresses over a few weeks.⁴¹ Both CTEPH and PTTM may present with features of PH and right heart failure on physical examination.⁴⁰ Other significant differences exist (see Table 8).

In PTTM, a chest radiograph may reveal reticulations and multiple pulmonary nodules; in CTEPH, there is cardiomegaly, dilatation of the right descending pulmonary artery, and opacified areas representing pulmonary infarction.⁴⁰ High-resolution CT scans may be able to differentiate

Table 8. Comparing clinical mimics CTEPH and PTTM.

	CTEPH	PTTM
<i>Clinical presentation</i>		
Clinical progression	Chronic	Acute to subacute
Dyspnea*	Common	Common
Cough*	Less common	Common
<i>Radiographic features</i>		
Chest CT [†]	Mosaicism Wedge-shaped infarcts Prominence of bronchial artery circulation	Ground-glass opacities Nodules Mediastinal/hilar adenopathy Septal thickening
<i>Hemodynamics</i> [‡]		
mPAP, mmHg (median)	47 (n = 669)	48 (n = 20)
PCWP, mmHg (median)	–	12 (n = 14)
PVR, dynes*s*cm ⁻⁵ (median)	709 (n = 604)	928 (n = 9)
Cardiac index, L/min/m ² (median)	2.2 (n = 632)	2 (n = 8)
<i>Histopathology</i> [§]		
Thromboemboli	Y	Y
Fibrocellular intimal proliferation	Y	Y
Involvement of pulmonary arterioles	Y	Y
Involvement of pulmonary venules	Y	Y
Presence of tumor cells	N	Y

*Symptoms of dyspnea can be seen in both; while cough is atypical in CTEPH, it is commonly noted in PTTM. Absence of these symptoms does not preclude either of the two disease entities.

[†]Radiographic information regarding CTEPH obtained from Gopalan et al.⁴⁰ Radiographic features of PTTM obtained from review of all cases included in this systematic review with radiographic information available.

[‡]Hemodynamic data obtained from Pepke-Zaba et al. CTEPH prospective international registry.⁴³

[§]Histopathology information regarding CTEPH obtained from Lang et al.⁴²

PTTM from CTEPH. In CTEPH, CT scanning often reveals diffuse mosaicism, wedge-shaped opacities (sometimes containing central cavitation) representing prior infarction, and prominence of the bronchial artery circulation.⁴⁰ In contrast, PTTM lacks all of the aforementioned features on chest CT with the most common findings described previously. V/Q scans may be abnormal in PTTM as well as CTEPH; however, in general, there is a paucity of data regarding the role of the V/Q scan in the diagnosis of PTTM. As such, the use of V/Q scan is unlikely to differentiate CTEPH and PTTM.

Hemodynamic assessment with echocardiography and RHC are appropriate in both conditions but unlikely to distinguish the two diseases.

The pathobiology of CTEPH includes thromboemboli, along with fibrocellular intimal proliferation, which is similar to that of PTTM.⁴² In PTTM, nests of tumor cells may also be seen within the thrombus. The hypothesized pathophysiology of PTTM is different than CTEPH in that it includes the release of various molecules such as VEGF, PDGF, and OPN directly by the tumor cells.²⁰

Interestingly, in large prospective registry data, 12.7% of patients with CTEPH also had a history of cancer.⁴¹ This registry data did not include histologic analysis of lung tissue from patients with CTEPH. However, in a manuscript

dedicated to examining the histopathology of CTEPH, including lung biopsies (n = 15) and autopsies (n = 16), there was no mention of the presence of tumor cells within the pulmonary vasculature.⁴³ In a case series of patients that underwent surgical thromboendarterectomy, tumor cells were not identified however the authors state that neoplastic embolic PH should be in the differential diagnosis of cases of chronic thromboemboli.⁴⁴

At present time, the aforementioned differences in clinical progression, the radiographic findings by high-resolution CT chest, and the histopathology demonstrating tumor cells within vessel lumen/wall and thrombi are the features which likely best distinguish PTTM from CTEPH. Though lung biopsy may help to differentiate CTEPH in patients with a history of cancer and PTTM, given the tenuous clinical status of such patients and high peri-operative risk of complications, obtaining lung biopsy is not recommended.

Treatment

A number of treatments have been attempted for patients diagnosed with or suspected of having PTTM. The challenge remains the low rate of ante-mortem diagnoses. While the average time to death from the onset of symptoms is approximately 9.5 weeks, a handful of publications do

report survival that is longer than what is expected with the natural progression of PTTM (Table 7). Among the important factors leading to a longer survival may be that the treatment regimen results in improvement in pulmonary pressures and/or cardiac output, in addition to treatment of the malignancy. One case report documented an improvement in mPAP from 48 mmHg to 34 mmHg after 16 days of treatment with imatinib, sildenafil, ambrisentan, total gastrectomy, and TS-1 chemotherapy (treatments were initiated at different time courses) with an eventual reduction in mPAP to 13 mmHg at four months.³⁰ In another case, after the initiation of treatment, there was an improvement in mPAP from 47 mmHg to 40 mmHg after 30 days, down to mid-20 mmHg after 90 days.³¹

Though selected reports have shown improvement in survival with the use of imatinib, there are reports of longer than expected survival without the administration of imatinib. In the first case, the patient received S-1 chemotherapy and cisplatin and survived 15 months after diagnosis.⁶ In the second case, the patient received S-1 chemotherapy, aspirin, warfarin, and dexamethasone and survived for at least seven months though further follow-up is not reported.¹⁰

Imatinib, as a PDGF receptor inhibitor, may have a role in reducing the vascular remodeling that promulgates PH. While it has shown promise by prolonging survival in some cases, its role may be limited to various factors including the type of primary malignancy; any further use ought to be studied more extensively.²⁰ Bevacizumab, a VEGF receptor inhibitor, has also been used in one case in conjunction with S-1 chemotherapy and imatinib—where the patient experienced a survival of 12 months after a diagnosis of PTTM.¹⁵ With the appropriate approval of institutional review boards, future studies aimed at improving survival in PTTM should be undertaken. Improved understanding of the pathobiology of the disease process may help generate more efficacious therapeutic targets.

Future directions

The prevalence of PTTM in autopsy case series of carcinoma is estimated at 1.4% in one report and 3.3% in another.^{1,2} In a gastric cancer autopsy case series, PTTM was found in 16.7% of cases.³ However, the true prevalence is unknown. Studies assessing for PH in patients with malignancy may provide an opportunity to understand the true prevalence and burden of this disease process. From our experience and the experience of others, the tumor emboli and resulting vasculopathy is not a diffuse process but rather the extent of pulmonary vascular stenosis appears to be heterogeneous.²⁸ Therefore, there may only be patchy findings on chest CT. We encourage clinicians to provide more detailed descriptions of the radiographic features and to describe the evolution of these features over time to better understand the evolution of the disease process. The location or distribution of nodules and ground-glass opacification (e.g. confined to one lobe, random versus centrilobular

and the extent of septal thickening (whether localized or encompassing multiple lobes of the lung) should be specified. A more quantitative analysis of the presence, distribution, and extent of the common radiographic features would be of significant value. In addition, we urge clinicians to consider elaborating on the assessment of PH, especially data gathered from the RHC, and, if available, hemodynamic assessment before and after the initiation of treatment. With continued improvement in our understanding of the pathobiology, we may yet identify new factors involved in the complex web of interactions that leads to the development of PH in PTTM.

Conclusion

PTTM is a clinicopathologic disease process with an extremely poor prognosis. This analysis provides a detailed examination of all the available published data that may help clinicians establish an earlier diagnosis of PTTM. The information contained herein will also hopefully allow providers to consider treatment options, in the context of clinical trials, in order to improve survival in this universally fatal disease process.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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