Pulmonary lymphangitic carcinomatosis (PLC) is a rare metastatic disease of the lungs characterized by diffuse infiltration and obstruction of the pulmonary lymphatic system by tumor cells.1, 2 Eighty percent of tumors spreading to the pulmonary lymphatic system in PLC are adenocarcinomas, with the most common primary sites being the breast, stomach, lung, pancreas, prostate, and colon.1, 2

High-resolution computed tomography (CT) of the chest in patients with PLC usually reveals thickening of the interlobular septa and central bronchovascular structures, known as central dots.3 Despite extensive involvement of the lymphatic system, the lung parenchyma usually appears normal and undistorted in CT findings, which is the distinguishing feature between lymphangitic carcinomatosis and sarcoidosis.4 Confirmatory diagnosis of PLC thus requires transbronchial or open-lung biopsy.2 The disease is associated with a poor prognosis given the extent of metastasis at the time of diagnosis; within 3 months of symptom onset, more than 50% of patients die.1

We describe the case of a 45-year-old woman who presented with cough and shortness of breath and who was initially diagnosed with a possible upper respiratory tract infection and treated with antibiotics as an outpatient. A subsequent hospital admission for worsening cough and dyspnea resulted in hypoxic respiratory failure and lung biopsy, which led to the diagnosis of PLC from metastatic signet ring cell gastric adenocarcinoma.
noma. Postulations regarding the mechanism of tumor cell spread through the lymphatic system as well as via signaling pathways are also discussed. To our knowledge, few cases of metastatic lymphangitic carcinomatosis have been reported. Because the present case describes how a pulmonary complaint resulted in the diagnosis of cancer of the gastrointestinal tract, it emphasizes the osteopathic principle of treating the patient as a whole and evaluating all organ systems.

Report of Case
A 45-year-old woman with a medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, and anemia secondary to menorrhagia presented to the emergency department with dry cough of 3 months duration. She had been seen in various outpatient clinics during the preceding 3 months, during which time bronchitis was diagnosed and she received multiple courses of antibiotic treatment (ciprofloxacin [500 mg orally twice per day] and erythromycin [250 mg orally every 6 hours]). At presentation, she described having fevers, with the highest being 102°F, as well as worsening cough and worsening dyspnea on exertion. Her surgical history was notable for a cesarean delivery. She denied smoking, drinking, or using illicit drugs. Her family history was notable for coronary artery disease and hypertension in her mother and diabetes in her father. Family history also included breast cancer in her aunt and ovarian cancer in her grandmother. She reported being up to date with her annual mammogram, the findings of which were within normal limits.

Her vital signs at the time of presentation were as follows: blood pressure, 153/82 mm Hg; heart rate, 120 min; respiratory rate, 28/min; temperature, 99.1°F; and oxygen saturation, 93% on 2 L nasal cannula. She appeared her stated age and was in mild distress secondary to tachypnea and notable use of accessory muscles. She remained alert and oriented to person, place, time, and situation. No evidence of lymphadenopathy was detected with palpation. Pulmonary examination revealed bilateral wheezing and crackling sounds. Cardiovascular examination revealed tachycardia with no murmurs. The rest of her physical examination findings were within normal limits, with no clubbing, cyanosis, or edema noted. A chest radiograph showed increased diffuse interstitial and airspace disease. Initial CT scan of the chest showed interlobular septal thickening with scattered ground glass opacification, as well as dilated arteries and mild nodularity along the fissures that suggested disease spread through the lymph channels and nodes.

She was admitted to the telemetry unit for sepsis secondary to pneumonia and received intravenous antibiotics. An echocardiogram obtained on day 7 of her hospital stay revealed an ejection fraction of 65% with a right ventricular systolic pressure of 46 mm Hg. Findings of pulmonary function tests revealed a moderate restrictive impairment without airflow limitations and a reduction in diffusing capacity. These findings were highly suggestive of either a ventilation-perfusion abnormality or a reduction in pulmonary capillary vs alveolar surface areas. Because of clinical suspicion of underlying pulmonary hypertension or pulmonary emboli, sildenafil (20 mg orally 3 times per day) and ambrisentan (5 mg orally daily) were added to her treatment regimen. Right-sided heart catheterization was performed shortly afterward, the findings of which confirmed the existence of pulmonary hypertension. Because of her worsening respiratory status, the patient was transferred to the intensive care unit, where she received mechanical ventilation via an endotracheal tube. A ventilation-perfusion scan showed findings compatible with intermediate probability for pulmonary embolism, and anticoagulant therapy was started. Despite these efforts, the patient’s fraction of inspired oxygen requirement continued to increase, raising the suspicion for superimposed interstitial lung disease or some source of malignancy.

The patient underwent an open-lung biopsy on day 17 of her hospital stay to rule out interstitial lung disease after a second CT scan of the chest showed a
Discussion
According to a review by Wu, PLC was first described in Europe in 1829 by Andral and later in 1874 by Troisier, who reported findings of pulmonary symptoms leading to diagnosis. Until 1936, French and German physicians reported similar cases with the majority of tumors originating from the stomach, breast, colon, lungs, and rectum. As noted by Hauser, it was not until the early 20th century that US authors began to publish cases involving lymphangitic carcinomatosis. Cases of metastatic PLC originating from lung, colon, and lip primary sites have since been published.

In lymphangitic carcinomatosis, symptoms of a primary cancer are usually absent or masked by pulmonary symptoms. As with our patient, cough and dyspnea are among the most common presenting symptoms of PLC. Sixty percent of patients present with cough, which is occasionally accompanied by sputum, ranging in appearance from white to blood tinged. Our patient’s physical examination findings did not reveal any signs of an oncologic process, consistent with literature that reports the absence of physical features in PLC. Chest radiographs of these patients can have distinct patterns, including thin stringy lines that branch out from the hilum, coarse bronchovascular markings, pleural effusions in 30% to 50% of cases, and hilar or mediastinal lymphadenopathy in 20% to 40% of cases. However, in 30% to 50% of patients, the chest radiograph usually appears normal. Our patient’s initial chest radiograph showed increased diffuse interstitial and airspace disease but was otherwise unremarkable. Sputum cultures are usually also misleading (ie, they may grow bacteria but are contaminants, not true infections) and lead to unnecessary antibiotics, as with our patient. Evidence of cor pulmonale or pulmonary hypertension is usually present at the time of diagnosis. Our patient exhibited subacute pulmonary hypertension with an echocardiographic right ventricular systolic pressure of 46 mm Hg and a right-sided heart catheterization, confirming the diagnosis. When infectious disease (eg, fungal, miliary...
tuberculosis), interstitial lung disease, and sarcoidosis have been ruled out in a patient with persistent cough and respiratory symptoms unresponsive to treatment, PLC should be considered.

As previously stated, the primary tumor sites of PLC include the following: breast (33%), stomach (29%), lungs (17%), pancreas (4%), and prostate (3%).\textsuperscript{1,2} Nonetheless, any metastatic neoplasm can cause PLC.\textsuperscript{12} Although the exact mechanism of action for metastatic spread is not yet understood, the tumor is believed to migrate by retrograde lymphatic permeation and growth along the lymphatic channels.\textsuperscript{5,13} Tumor cells can spread along the paraesophageal lymphatic vessels through the hilum into the lung parenchyma, causing the development of pulmonary symptoms.\textsuperscript{5} The invasion of the lymphatic vessels by the neoplastic cells causes compression of the bronchioles and alveoli, as well as thickening of bronchovascular bundles and septa, leading to dyspnea and cough.\textsuperscript{2,5} These symptoms, in turn, can lead to the development of pulmonary hypertension, cor pulmonale, or pulmonary emboli if PLC is not diagnosed early. If the neoplastic cells spread outside the interstitium and lymphatic spaces into the lung parenchyma, a nodular pattern can result.\textsuperscript{2,11} Our patient had evidence of this septal thickening and nodularity consistent with literature findings.

Das et al\textsuperscript{14} postulated the involvement of vascular endothelial growth factor C (VEGF-C) in the metastasis of primary tumors, leading to lymphangitic carcinomatosis. In studies of mice, they showed that VEGF-C facilitates distant metastases by promoting lymphangiogenesis at the primary site of tumor through the VEGF-C/vascular endothelial growth factor receptor-3 signaling pathway.\textsuperscript{14} By altering lung tissue, VEGF-C contributes to aggressive lymphatic spread to the lymph nodes. Das et al’s observations\textsuperscript{14} of VEGF-C in mice correspond to VEGF-C’s role in lymphangitic carcinomatosis in humans. The metastatic pattern that results is most evident in airways, including the formation of pulmonary emboli, the
promotion of intralymphatic tumor spread, the dilation of pulmonary lymphatics, and the promotion of further lymphangiogenesis. On the basis of these findings, Das et al postulated that altering the signaling pathway or producing antibodies against certain receptors along the pathway may potentially have beneficial results in cancer patients.

In addition to contributing to lymphangiogenesis, VEGF induces endothelial proliferation. With tissue factor (TF), VEGF plays a pivotal role in the spread of primary tumors to the lymphatic systems of the lungs, especially in signet ring cell carcinoma of the stomach. Both VEGF and TF induce endothelial and intimal proliferation, respectively. Intimal proliferation in pulmonary vessels causes aggregation of platelets and the release of serotonin (5-hydroxytryptamine [HT]) from the platelets' granules, contributing to thrombogenesis and vascular remodeling. When the intimal myofibroblasts proliferate, they express 5-HT2A receptors that bind the released 5-HT. With the activation of a signaling pathway involving protein kinase C and mitogen-activated protein/extracellular signal-regulated kinases, further myofibroblast proliferation, tissue fibrosis, formation of microthrombi, and tumor emboli occur. This phenomenon, known as pulmonary tumor thrombotic microangiopathy, can cause subacute pulmonary hypertension as a result of cancer cells invading the pulmonary vasculature. Pulmonary tumor thrombotic microangiopathy is a rare complication of poorly differentiated adenocarcinomas, especially in signet ring cell carcinoma of the stomach. Research on the development of 5-HT2A receptor antagonists is in process, which may lead to more treatment options and a better prognosis for these patients. Our patient’s subacute pulmonary hypertension and microthrombotic tumor emboli from gastric signet ring cell adenocarcinoma likely contributed to the development of PLC.

Even with early diagnosis, prognosis is poor for PLC patients, especially in cases with signet ring cell gastric adenocarcinoma. Gastric adenocarcinoma accounts for 8% of newly diagnosed cancers worldwide and by itself is associated with poor prognosis. According to the American Cancer Society, 5-year survival rates for patients with gastric adenocarcinoma depend on the stage at the time of diagnosis and are as follows: stage IA, 71%; stage IB, 57%; stage IIA, 45%; stage IIB, 33%; stage IIIA, 20%; stage IIIB, 14%; stage IIIC, 9%; and stage IV, 4%. However, in a case report by Kikuchi et al, cisplatin was shown to be promising in extending progression-free survival.

Pulmonary lymphangitic carcinomatosis shares similar characteristics to sarcoidosis and interstitial lung disease and can be misdiagnosed as either, both of which were in the differential diagnosis for our patient. Although these diseases can present with nodular patterns on chest CT scans, the nodules of sarcoidosis are usually confined to the upper as opposed to the lower lobes in PLC. Biopsy is required to differentiate between the 2 because it confirms the absence or presence of noncaseating granulomas. Definitive pathologic diagnosis is also needed to rule out the possibility of interstitial lung disease.

Our patient had unique features of PLC, including involvement of the antrum of the stomach and metastasis to bone at the time of presentation. Pulmonary lymphangitic carcinomatosis is an extremely rare manifestation of gastric adenocarcinoma and is seen in a very small percentage of adults with metastatic gastric carcinoma.

Conclusion
As demonstrated in the present case, it is important for physicians to treat the whole patient and evaluate all organ systems. Physicians should consider PLC in patients who present with pulmonary symptoms, who are unresponsive to antibiotics, and in whom other pulmonary infections have been ruled out. Because pulmonary manifestations are the usual presenting symptoms of PLC, a thorough malignancy workup is needed to
delineate the primary site of tumor once infectious disease has been ruled out. Because of the unique mechanism of the spread of tumor, subacute pulmonary hypertension and pulmonary tumor thrombotic microangiopathy are frequent complications encountered by the disease process. Although PLC is generally associated with an extremely poor prognosis, early diagnosis and implementation of palliative platinum-based chemotherapy may lead to progression-free survival.

References