CASE REPORT

Pulmonary Tumor Thrombotic Microangiopathy due to Advanced Gastric Cancer with Virchow’s Node Metastasis

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Summary
Pulmonary tumor thrombotic microangiopathy (PTTM) is a fatal cancer-related complication characterized by severe progressive pulmonary hypertension. Antemortem diagnosis is difficult owing to the rapid progression of the condition, especially when the patient has no known malignancies and initially presents with pulmonary hypertension. Here we report a case of PTTM due to occult gastric cancer with metastasis in the left supraclavicular lymph node, also known as Virchow’s node. Enlarged Virchow’s node is an important indicator of advanced gastric cancer. In patients with progressive pulmonary hypertension of unknown origin, enlarged Virchow’s node can be an important indicator for the diagnosis of PTTM.

Key words: Pulmonary hypertension, Metastatic cancer

Pulmonary tumor thrombotic microangiopathy (PTTM) is a fatal cancer-related complication characterized by severe progressive pulmonary hypertension. The majority of PTTM cases reported are associated with gastric cancer. Antemortem diagnosis is extremely difficult because of the rapid progression of PTTM, especially when the patient has no known malignancies and initially presents with pulmonary hypertension. As the enlargement of the left supraclavicular lymph node, also known as Virchow’s node, is one of the important signs of advanced gastric cancer, Virchow’s node enlargement can suggest the diagnosis of PTTM. Here, we report a case of PTTM complicated by advanced gastric cancer with Virchow’s node metastasis.

Case Report
The patient was a 65-year-old woman with a history of thyroid medullary carcinoma that was successfully resected two years ago; she had no history of smoking. She had been experiencing weight loss and dry cough for eight months. She had developed gradually worsening dyspnea on exertion, one month earlier. On examination at a nearby hospital, her oxygen saturation was 92%, with an increased level of fibrinogen degradation product (FDP; 75 μg/mL); echocardiography revealed a “D-shaped” left ventricle. The patient was suspected to be suffering from acute pulmonary embolism and was transferred to our hospital.

At admission, her body temperature was 36.1°C, blood pressure was 180/80 mm Hg, heart rate was 83 bpm, respiratory rate was 16 breaths per minute, and oxygen saturation was 93% with oxygen supplementation at 3 L/minute. Physical examination revealed an increased intensity of second heart sound with no murmurs or rales. Only a rough palpation of systemic lymph nodes was performed, and enlargement of the left supraclavicular lymph node was not noticed. Laboratory examination showed mild thrombocytopenia (10.2 × 10^4/μL) and increased biliary enzymes (gamma-glutamyl transpeptidase 103 IU/L; alkaline phosphatase 802 IU/L). Her hemoglobin concentration was within the normal range (12.6 g/dL). Coagulation test showed prolonged prothrombin time (15.3 seconds), with an increased level of FDP (32.0 μg/mL), D-dimer (24.1 μg/mL), thrombin-antithrombin complex (32.0 ng/mL), and plasmin-alfa-2 plasmin inhibitor complex (101 μg/mL), and a decreased level of fibrinogen (97 mg/dL). Electrocardiography, chest radiography, and transthoracic echocardiography showed signs of pulmonary hypertension with preserved left ventricular systolic function (Figure 1). A contrast-enhanced computed tomography (CT) was immediately performed, but no emboli were detected in the pulmonary arteries. Instead, enlarged paraaortic lymph nodes and enlarged Virchow’s lymph node (1.3 cm × 1.5 cm) were observed (Figure 2). The patient was diagnosed with pulmonary hypertension of unknown origin and was started on anticoagulation therapy, while undergoing further examination. Her condition was stable for the first three days; however, her symptoms gradually worsened from Day 4 onwards. On Day 6, her blood pressure dropped to 89/48 mm Hg and she was unable to move from her bed. Subsequently, she was transferred to the intensive care unit and underwent right heart catheterization. Her pulmonary artery pressure was 84/41 mm Hg.
(mean, 54 mm Hg) with a pulmonary vascular resistance of approximately 20 wood units. Cardiac output was 2.0 L/minute, while the mean pulmonary arterial wedge pressure was 13 mm Hg. Echocardiographic estimation of the parameters showed similar results. The patient was diagnosed with right cardiac failure due to severe pulmonary hypertension and started on a continuous infusion of dobutamine.

Subsequently, progressive pulmonary hypertension along with the para-aortic and Virchow’s lymph node enlargement, suggestive of malignancy, led us to suspect PTTM due to occult gastric cancer. Pulmonary microvascular cytology was performed, but atypical cells were not detected. Carcinoembryonic antigen and carbohydrate antigen 19-9 levels were in the normal range (1.3 ng/mL and 9.2 IU/mL, respectively). Lung biopsy and gastric fi-
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PTTM WITH VIRCHOW’S NODE METASTASIS

Figure 3. Signet ring cells were observed in the gastric cancer (A: ×20). Metastasis of adenocarcinoma was found in the enlarged Virchow’s lymph node (B: ×20).

Figure 4. Fibrocellular intimal proliferation occluded the lumen of the pulmonary artery, approximately 830 μm in diameter (Hematoxylin-eosin double stain and elastic Van Gieson’s stain, ×10).

Post-mortem examination revealed poorly differentiated adenocarcinoma with signet ring cells in the anterior wall of the stomach (Figure 3A). Miliary metastases were found in the left adrenal gland and the dura mater. Systemic lymph node metastasis, including the para-aortic and Virchow’s lymph node metastasis, was observed (Figure 3B). In the lungs, marked fibrocellular intimal proliferation of small pulmonary arteries, compatible with PTTM, was observed (Figure 4). Thickening of the right ventricular wall, indicative of pulmonary hypertension, was also observed.

Discussion

The present report describes a case of fatal progressive pulmonary hypertension due to PTTM, complicated by occult gastric cancer with Virchow’s node metastasis. Although antemortem diagnosis and treatment were not possible, the enlargement of Virchow’s lymph node led us to suspect PTTM.

PTTM is a rare complication of cancer, first described by von Herbay, et al. in 1990. PTTM is histologically characterized by non-occluding microscopic tumor cell emboli accompanied by marked fibrocellular intimal proliferation of small pulmonary arteries, resulting in stenosis and occlusion of the arteries.\textsuperscript{1} It is clinically
characterized by fatal and rapidly progressive pulmonary hypertension, as observed in the present case. Uruga, et al. reported that the median survival time after the initiation of oxygen supplementation was nine days.\(^5\) Owing to this rapid progression and the under-recognition of the disease, antemortem diagnosis is difficult, especially when the patient initially presents with pulmonary hypertension with no known malignancies. This condition is frequently accompanied by coagulation disorders and thrombocytopenia, mimicking pulmonary embolism.\(^6,7\) However, as observed in the present case, contrast-enhanced CT shows no signs of emboli in the pulmonary arteries. In such cases, PTTM should be suspected.

A definite diagnosis of PTTM can be made by lung biopsy; however, lung biopsy is often difficult to perform in a deteriorating patient. Detection of tumor cells by pulmonary microvascular cytology has been reported as an alternative method,\(^8,9\) but it was not useful in our case. Considering the rapid progression of PTTM, it is pragmatic to initiate possible therapy if the disease is suspected and a comorbid adenocarcinoma is confirmed.

Gastric cancer, especially poorly differentiated adenocarcinoma, is most frequently associated with PTTM.\(^10,11\) It is noteworthy that severe lymphatic invasion and abdominal lymph node metastasis of the primary tumor is often observed in patients with PTTM.\(^12\) Growth factors, such as platelet-derived growth factor and vascular endothelial growth factor, have been reported to play a certain role in the pathophysiology of pulmonary hypertension.\(^13,14\) Previous studies have demonstrated that these molecules are frequently expressed in gastric cancer with lymphatic invasion and lymph node metastasis.\(^15,16\) Although the causality and the mechanism of the association have not yet been elucidated, this may partially explain why patients with PTTM frequently have severe lymphatic invasion and lymph node metastasis. To the best of our knowledge, there are no reports focusing on Virchow’s lymph node metastasis in a patient with PTTM; however, it is plausible to speculate that Virchow’s lymph node metastasis can be observed in a certain proportion of patients with PTTM. This also emphasizes the importance of routine physical examination, including palpation of systemic lymph nodes.

Owing to the late recognition of the importance of Virchow’s node enlargement in the present case, we could not perform fine needle aspiration cytology. Fine needle aspiration cytology of the node is a useful low-invasive procedure for the initial evaluation of the enlarged node and the specific diagnosis of metastatic carcinoma.\(^17\) Earlier recognition of the possibility of PTTM may have led to an antemortem diagnosis and treatment. Treatment for PTTM has not been established, but several case reports suggest the utility of molecular-target drugs such as imatinib and chemotherapy for the treatment of primary cancer.\(^18,19\) Patients in some cases were reported to have survived for as long as one year.\(^20,21\)

Therapies targeting pulmonary hypertension, such as inhalation of nitric oxide and systemic administration of pulmonary vasodilators, may have been an option. However, these treatments have been reported to be ineffective, probably because of the progressive nature of the disease, and were not attempted in our case.\(^22\)

Here, we have described a patient with PTTM due to advanced gastric adenocarcinoma with Virchow’s node metastasis. In patients with pulmonary hypertension of unknown origin, it is important to search for signs of cancer, including Virchow’s node enlargement. In cases with Virchow’s node enlargement, fine needle biopsy may be an option to approach the diagnosis of PTTM.

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Disclosures

Conflicts of interest: None.

References

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