Trousseau Syndrome and the Unknown Cancer: Use of Positron Emission Tomographic Imaging in a Patient With a Paraneoplastic Syndrome

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Trousseau syndrome is defined as a migratory thrombophlebitis found typically in patients with an underlying malignancy. Conventional diagnostic testing and imaging can be used to successfully diagnose a primary malignancy in approximately 85% to 95% of patients. However, along with a comprehensive medical history and physical examination, numerous tests are frequently required, including blood tests, tumor markers, chest radiography, upper endoscopy, and computed tomography of the chest, abdomen, and pelvis. We present a case in which positron emission tomographic imaging was important for diagnosing the malignancy underlying Trousseau syndrome. Positron emission tomography may play an important role in the efficient evaluation of such cases.

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CT = computed tomography; DVT = deep venous thrombosis; FUO = fever of unknown origin; GI = gastrointestinal; PET = positron emission tomography

When an underlying malignancy is strongly suspected, the inability to determine the presence or origin of the neoplasm despite extensive investigations produces diagnostic, prognostic, and therapeutic uncertainty for physicians and patients. We describe a patient with constitutional symptoms and Trousseau syndrome (ie, migratory thrombophlebitis occurring primarily as a paraneoplastic syndrome) for whom positron emission tomography (PET)–guided biopsy led to a diagnosis of the underlying malignancy.

REPORT OF A CASE

A 51-year-old man who was a smoker was referred for evaluation and treatment of recurrent deep venous thromboses (DVTs) and management of anticoagulation. Two months previously, the patient had presented with abdominal discomfort, night sweats, and a 9-kg weight loss. Physical examination findings were unremarkable, and a complete blood cell count, electrolyte panel analysis, liver function tests, urinalysis, and chest radiography did not confirm a diagnosis. Upper endoscopy with biopsy revealed gastric erosions presumed to be secondary to nonsteroidal anti-inflammatory drug therapy; these agents were discontinued. Two weeks later, the patient noticed progressive asymmetrical lower extremity edema with associated superficial thrombophlebitis. Findings on ultrasonography of the lower extremities were unremarkable. Computed tomography (CT) of the chest, abdomen, and pelvis revealed an indistinct 1-cm left apical fluffy nodule, nonpathologically enlarged hilar and mediastinal lymph nodes, and bilateral renal infarctions. During the next few days, increasing edema in the left lower extremity prompted further imaging, which confirmed DVT. Enoxaparin and subsequently warfarin treatments were initiated. Despite careful monitoring and warfarin dosage adjustment, the patient developed superficial thromboses and DVTs in both upper extremities. He was admitted to the hospital for further evaluation and management of anticoagulation.

On admission, the patient reported edema, abdominal bloating, early satiety, constipation, and pain at the site of inflamed and thrombosed superficial veins. His weight had been stable since discontinuation of nonsteroidal anti-inflammatory drug therapy. His history included 60 pack-years of smoking, alcohol abuse in the remote past, vasectomy, and hemorrhoids. The patient's family history was remarkable for an uncle with DVT and his father with prostate cancer.

Examination of the patient revealed an anxious, cachectic-looking man in no acute distress. His blood pressure was 119/81 mm Hg, respiratory rate was 20/min, temperature was 36.5 C, and heart rate was 100 beats/min and regular. Peripheral edema was noted bilaterally, with numerous palpable, painful, and erythematous superficial cords in both the upper and the lower extremities (Figure 1). Results from the patient's testicular examination were normal. There was no evidence of any lymphadenopathy or organomegaly. Findings on the rest of his examination were unremarkable.

Unfractionated intravenous heparin was initiated, and repeated ultrasonography of the lower extremities confirmed multiple DVTs. Because of the patient's gastrointestinal (GI) symptoms, he underwent both upper and lower GI endoscopic examinations, findings of which were unremarkable. Serum protein electrophoresis performed before hospitalization showed a monoclonal protein. Bone

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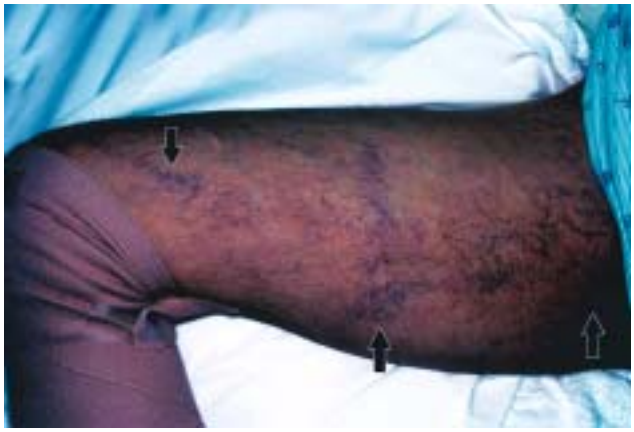

FIGURE 1. The painful, raised, erythematous palpable cords (arrows) of migratory superficial thrombophlebitis seen on physical examination.

marrow biopsy specimens revealed a plasma cell disorder with a 10% to 30% involvement of monoclonal λ plasma cells with normal trilineage hematopoiesis and cytogenetics. The patient's paraneoplastic panel (including antineuronal nuclear antibodies, Purkinje cell cytoplasmic antibodies, amphiphysin antibodies, collapsin response-mediator protein-5-IgG antibodies, striated muscle antibodies, calcium channel binding antibodies, and acetylcholine receptor binding antibodies) was normal, and his β_2-microglobulin level was slightly elevated at 1.84 μg/mL. Because Trousseau syndrome is not strongly associated with plasma cell disorders, we intended to perform a video-assisted thorascopic surgical biopsy of the only other abnormality found with conventional imaging, the lung nodule. Before the planned biopsy, PET revealed a hypermetabolic mediastinal lymph node (Figure 2) and paradoxically little activity in the lung nodule. An inferior vena cava filter was inserted before the patient underwent video-assisted thorascopic surgical biopsy and mediastinoscopy. The lung nodule noted on CT was not palpable or identifiable during the biopsy and was believed to be due to scarring. Results from biopsy of the lymph node revealed a metastatic grade 4/4 adenocarcinoma in a sinusoidal pattern. The keratin staining pattern suggested a possible primary neoplasm of the lung or upper GI tract. The patient was discharged from the hospital. Radiation therapy and chemotherapy were initiated for a presumed non–small cell lung cancer.

DISCUSSION

Malignancy and thromboembolism are associated closely. Venous thromboembolism is increased 4-fold in patients with cancer, and underlying malignancy accounts for 10% to 20% of causes of DVT.[1-3] Proposed mechanisms include changes in antithrombotic and prothrombotic proteins, cytokine activation, and endothelial dysfunction, conditions that can lead to chronic disseminated intravascular coagulation.[4-8] Armand Trousseau,[9] who first described the association between migratory thrombophlebitis and visceral malignancy, said thrombophlebitis is often the initial sign of underlying malignancy. Speaking at the Hotel-Dieu de Paris in 1865, he noted, "I have long been struck by the frequency with which cancerous patients are affected with painful edema of the superior and inferior extremities.... I have since had the opportunity of observing other cases of painful edema, in which at autopsy, I found visceral cancer but in life, there was no appreciable cancerous tumor. The remarks which I have made on the frequency of phlegmasia in cancerous patients necessitates for you, gentlemen, to search for cancer in these situations."[9,10] Interestingly, Trousseau himself subsequently presented with the syndrome he described and died of gastric carcinoma.

Malignancies most commonly associated with Trousseau syndrome include those of the pancreas, lung, prostate, stomach, and colon, with pancreatic cancer accounting for 50% of all cases.[11] Whether extensive screening for malignancy in idiopathic DVT is warranted in asymptomatic patients is controversial; however, most authorities follow Trousseau's admonition to search for an underlying malignancy when presented with migratory thrombophlebitis of otherwise undetermined origin.

On the basis of pooled data, the odds ratio of malignancy in patients with DVT compared with that in patients without DVT is 3.2.[12] Moreover, the risk of recurrent DVT in such patients is substantially higher.[13] Therefore, some researchers have advocated more extensive evaluations than history and physical examination alone for patients with idiopathic DVT, including CT of the lungs, abdomen, and pelvis and endoscopic examination of the GI tract.[14-16] The hope is to identify and optimize treatment of the underlying neoplasm, which is ultimately found after exhaustive testing in 85% to 95% of these patients.[13,14,17,18] In our patient, an extensive search for a neoplasm had begun before hospitalization became necessary and continued concurrently with early hospital stay. Ultimately, PET was helpful in guiding biopsy. Speculatively, earlier use of PET in the search for malignancy could have prevented many other less fruitful tests.

Prior studies have shown the accuracy of PET with fluorodeoxyglucose F 18 in diagnosing, staging, and, therapeutic monitoring of cancers of the head and neck, lungs, breast, and colorectum; lymphomas; and melanomas. Extremely few studies have examined the utility of PET in patients presenting with paraneoplastic syndrome; none were conducted in patients with migratory thrombophlebi-

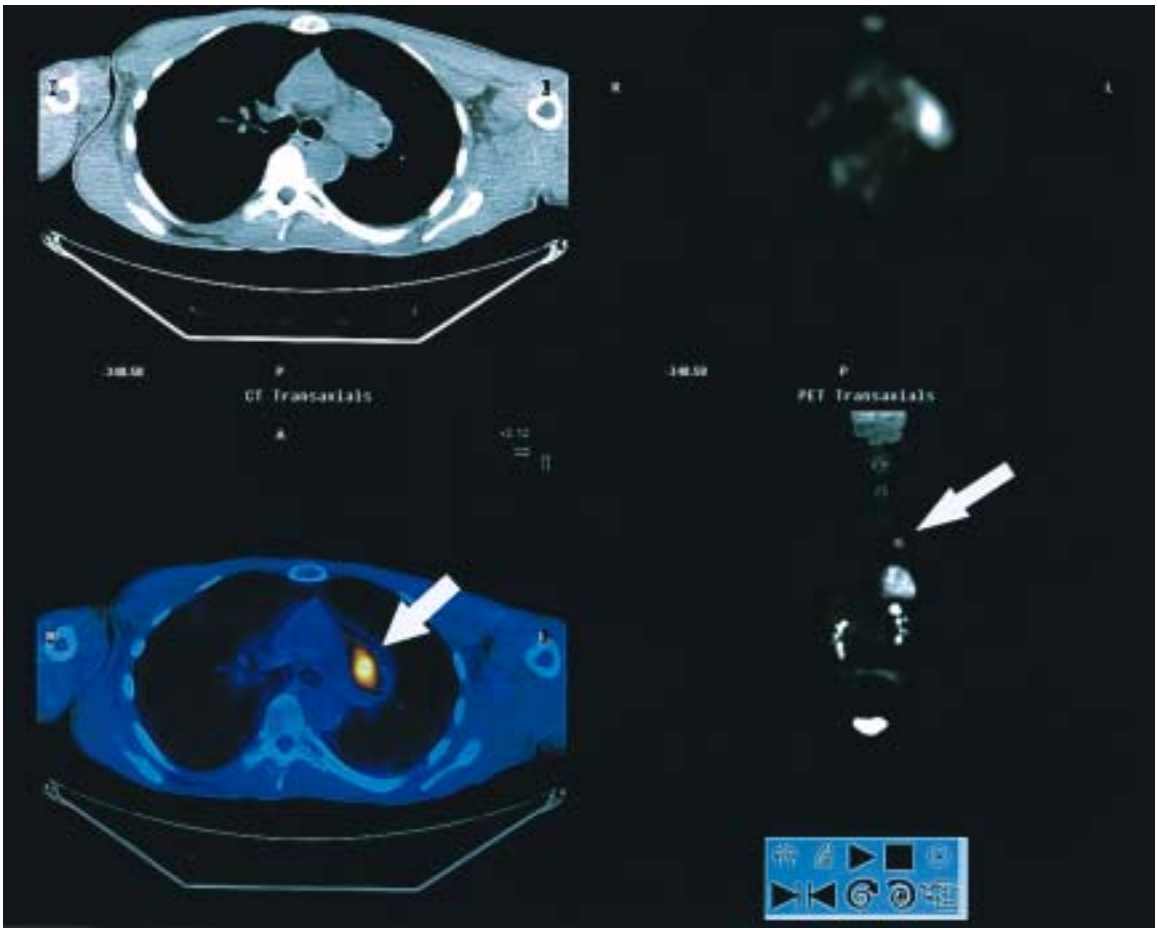

FIGURE 2. Computed tomogram (CT) (upper left) shows some bulkiness in the left hilar region, with an area of hypermetabolic activity within a large lymph node (arrow) identified on the CT/positron emission tomogram (PET) image fusion (lower left); PET (right) confirms this area (arrow) in the mediastinal region. A = anterior; L = left; P = posterior; R = right.

tis.[19,20] However, PET has been useful for patients presenting with cancer of unknown primary origin and more recently for diagnosing malignancy in patients with fever of unknown origin (FUO).

In a meta-analysis evaluating the diagnoses of primary malignancy in 298 patients with cancer of unknown primary origin, PET showed a sensitivity of 0.87 (95% confidence interval, 0.81-0.92) and a specificity of 0.71 (95% confidence interval, 0.64-0.78).[21] In several series using nonfunctional imaging, a primary tumor was not localized in 70% to 80% of patients with cancer of unknown primary origin; PET suggested the diagnosis in an additional 30% to 40% of patients with cancer of unknown primary origin.[22-24] Interestingly, the likelihood of subsequent primary cancer after a normal PET scan is minimal.[23-25]

For patients with FUO, PET has been advocated as an adjunct to tools currently used to search for underlying neoplastic, infectious, and autoimmune disorders. Sensitivity and specificity are lower than those found in cancer of unknown primary origin, at 50% and 46%, respectively.[26] The study by Lorenzen et al[27] of 16 patients with FUO showed that PET led to correct diagnosis in 11 patients (69%) and had a high negative predictive value for subsequent specific etiology. A larger study by Blockmans et al[28] showed that PET helped establish a diagnosis in 41% of their 58 patients.

The cost per patient of whole-body PET with fluorodeoxyglucose F 18 is approximately $2000 to $3000 (US). In our patient, the combined costs of other evaluations (CT, GI endoscopy and biopsy, bone marrow biopsy, blood tests, and manipulation of anticoagulation to facilitate safe testing) far exceeded this amount. Therefore, we suggest that PET be considered early in the evaluation of patients with Trousseau syndrome because PET may be more efficient, less invasive, and more cost-efficient. A trial to evaluate this strategy prospectively is needed.

REFERENCES

1. Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer [published correction appears in *Lancet*. 2000; 355:758]. *Lancet*. 1998;351:1077-1080.

2. Lee AYY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation*. 2003;107(23, suppl 1):I17-I21.

3. Prandoni P, Lensing AWA, Büller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med*. 1992;327: 1128-1133.

4. Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisted. *Blood*. 1983;62:14-31.

5. Karpatkin S, Pearlstein E. Role of platelets in tumor cell metastases. *Ann Intern Med*. 1981;95:636-641.

6. Nanninga PB, van Teunenbroek A, Veenhof CH, Buller HR, ten Cate JW. Low prevalence of coagulation and fibrinolytic activation in patients with primary untreated cancer. *Thromb Haemost*. 1990;64:361-364.

7. Dvorak HF. Thrombosis and cancer. *Hum Pathol*. 1987;18:275-284.

8. Sack GH Jr, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. *Medicine (Baltimore)*. 1977; 56:1-37.

9. Trousseau A. *Clinique Médicale de l'Hôtel-Dieu de Paris*. Vol 3. 2nd ed. Paris, France: JB Baillière; 1865:654-712.

10. Tisdale JF, Snowden TR, Johnson DR. Case report: poorly differentiated carcinoma of unknown primary presenting as Trousseau's syndrome. *Am J Med Sci*. 1995;309:183-187.

11. Pinzon R, Drewinko B, Trujillo JM, Guinee V, Giacco G. Pancreatic carcinoma and Trousseau's syndrome: experience at a large cancer center. *J Clin Oncol*. 1986;4:509-514.

12. Prins MH, Hettiarachchi RJ, Lensing AW, Hirsh J. Newly diagnosed malignancy in patients with venous thromboembolism: search or wait and see? *Thromb Haemost*. 1997;78:121-125.

13. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100:3484-3488.

14. Monreal M, Lafoz E, Casals A, et al. Occult cancer in patients with deep venous thrombosis: a systematic approach. *Cancer*. 1991;67:541-545.

15. Cornuz J, Pearson SD, Creager MA, Cook EF, Goldman L. Importance of findings on the initial evaluation for cancer in patients with symptomatic idiopathic deep venous thrombosis. *Ann Intern Med*. 1996;125:785-793.

16. Bastounis EA, Karayiannakis AJ, Makri GG, Alexiou D, Papalambros EL. The incidence of occult cancer in patients with deep venous thrombosis: a prospective study. *J Intern Med*. 1996;239:153-156.

17. Hettiarachchi RJK, Prins MH, Büller HR, Prandoni P, ten Cate JW. Occult malignancy in patients with deep-vein thrombosis: incidence and risk indicators [abstract]. *Thromb Haemost*. 1997;77(suppl):383. Abstract OC-1563.

18. Aderka D, Brown A, Zelikovski A, Pinkhas J. Idiopathic deep vein thrombosis in an apparently healthy patient as a premonitory sign of occult cancer. *Cancer*. 1986;57:1846-1849.

19. Berner U, Menzel C, Rinne D, et al. Paraneoplastic syndromes: detection of malignant tumors using [^{18}F]FDG-PET. *Q J Nucl Med*. 2003;47:85-89.

20. Crotty E, Patz EF Jr. FDG-PET imaging in patients with paraneoplastic syndromes and suspected small cell lung cancer. *J Thorac Imaging*. 2001; 16:89-93.

21. Delgado-Bolton RC, Fernández-Pérez C, González-Maté A, Carreras JL. Meta-analysis of the performance of ^{18}F-FDG PET in primary tumor detection in unknown primary tumors. *J Nucl Med*. 2003;44:1301-1314.

22. Rades D, Kuhnel G, Wildfang I, Borner AR, Schmoll HJ, Knapp W. Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management. *Ann Oncol*. 2001;12:1605-1609.

23. Bohuslavizki KH, Klutmann S, Kroger S, et al. FDG PET detection of unknown primary tumors. *J Nucl Med*. 2000;41:816-822.

24. Lassen U, Daugaard G, Eigtved A, Damgaard K, Friberg L. 18F-FDG whole body positron emission tomography (PET) in patients with unknown primary tumours (UPT). *Eur J Cancer*. 1999;35:1076-1082.

25. Lonneux M, Reffad A. Metastases from unknown primary tumor: PET-FDG as initial diagnostic procedure? *Clin Positron Imaging*. 2000;3:137-141.

26. Kjaer A, Lebech A-M, Eigtved A, Højgaard L. Fever of unknown origin: prospective comparison of diagnostic value of ^{18}F-FDG PET and ^{111}In-granulocyte scintigraphy. *Eur J Nucl Med Mol Imaging*. 2004;31:622-626.

27. Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. *Nucl Med Commun*. 2001;22:779-783.

28. Blockmans D, Knockaert D, Maes A, et al. Clinical value of [^{18}F]fluorodeoxyglucose positron emission tomography for patients with fever of unknown origin. *Clin Infect Dis*. 2001;32:191-196.