

Trousseau's Syndrome Mimicking Severe Bilateral Peripheral Arterial Disease

Aritz Gil-Ongay¹, María Elena Arnáiz-García², Cristina Blanco-Castillo³, Ivana Pulitani³, José María González-Santos², Ana María Arnáiz-García⁴

¹ Department of Cardiology, University Hospital Marqués de Valdecilla, Santander, Spain

² Department of Cardiovascular Surgery, University Hospital of Salamanca, Salamanca, Spain

³ Department of Cardiovascular Surgery, University Hospital Marqués de Valdecilla, Santander, Spain

⁴ Department of Internal Medicine and Infectious Diseases, University Hospital Marqués de Valdecilla, Santander, Spain

Received: 11 Jan. 2017; Accepted: 18 Apr. 2017

Abstract- We present the case of how a massive proximal deep vein thrombosis result of an unknown recurrence of a previously colonic malignancy treated, classically known Trousseau's Syndrome, can mimic symptoms of severe peripheral arterial disease in a patient affected of peripheral chronic arterial disease surgically treated. Trousseau's Syndrome is commonly associated with serious and chronic diseases and a variety of paraneoplastic thromboembolic disorders. Thrombotic episodes may precede the diagnosis of cancer and be the potential marker for an unknown and occult malignancy. We highlight the key points of the Trousseau Syndrome and those paraneoplastic vasculopathies related that can mimic a vascular disease or complication.

© 2018 Tehran University of Medical Sciences. All rights reserved.

Acta Med Iran 2018;56(6):415-418.

Keywords: Peripheral arterial disease; Deep venous thrombosis; Cancer; Syndrome of trousseau

Introduction

Thrombotic episodes can be the first manifestation of an unknown or hidden neoplasia. A variety of paraneoplastic thromboembolic disorders, involving the veins, arteries, or both entities have been described and termed Trousseau's Syndrome. However, the form of presentation of Trousseau's Syndrome can also mimic an acute ischemic peripheral event or complication overall in patient affected of chronic vascular diseases. This uncommon presentation and lack of suspicion can lead to a misdiagnosis and delayed treatment with deadly consequences. Herein we describe the case of a Trousseau's Syndrome manifested as massive vein thrombosis mimicking a peripheral ischemic arterial compromise.

Case Report

A 74-year-old with a previous history of hypertension, type 2 diabetes mellitus and colonic adenocarcinoma (stage pT3pN2b) treated surgically with sigmoid colectomy plus chemotherapy two years before was admitted to our institution. Any local or distal recurrence of tumor had been detected during the follow

up to the present.

As previous arterial vascular events, he was diagnosed of a chronic and peripheral arterial disease five years before. An inverted right femoro-popliteal saphenous vein bypass was successfully done at that moment. Since surgery, the evolution was unremarkable. However, during last three months patient referred with critical intermittent claudication of left leg and he was scheduled for a left femoro-popliteal bypass with inverted saphenous vein. Surgery achieved a satisfactory result. Oral anti-aggregation with acetylsalicylic acid (100 mg/24h) and prophylactic anticoagulation with subcutaneous low weight heparin (Enoxaparin 40 mg/24h) was started in the early postoperative period. The patient recovered well. However, five days postoperatively, the patient suddenly worsened with an acute infra-abdominal pain. Vital signs revealed a blood pressure of 114/68 mm Hg, a body temperature of 36.8° C and a heart rate of 104 beats per min. A respiratory rate of 14 breaths per min was detected, with an oxygen saturation of 97% on room air. Findings from examinations of the abdomen showed diffuse pain in his abdomen, focused in the lower quadrants. The surgical wounds in his left leg result of recent peripheral bypass showed good aspect, however a painful edema appeared

Corresponding Author: M. Elena Arnáiz-García

Department of Cardiovascular Surgery, University Hospital of Salamanca, Salamanca, Spain
Tel: +34 92 3291263, Fax: +34 923291263, E-mail address: elarnaiz@hotmail.com

in both lower extremities. Both legs turned to pale and no palpable peripheral pulses were found in the physical examination.

The electrocardiogram showed sinus tachycardia at 110 beats per minute and chest radiograph was unremarkable. Laboratory blood test showed normocytic anemia, leucocytosis and thrombocytosis. A high leukocyte (13.5×10^3 cells/ml) and platelet counts (5×10^5 cells/ml) was detected. Coagulation studies were within normal limits, and hypercoagulable workup was also normal. The values of D dimer were high (1500 ng/ml). Specific tests for hypercoagulability disorders included activated protein C resistance, anticardiolipin antibody, antithrombin III, basal homocysteine, complete blood count (with examination of the peripheral smear), D dimer, Factor V Leiden, fibrinogen, lupus anticoagulant, partial thromboplastin time, protein S, prothrombin time, and thrombin time. Results were normal for all of these studies.

In order to discard an acute bypass complication such as bleeding or acute thrombosis, an angio-CT Scan was performed. It revealed extended thrombosis of the deep venous system spreading from iliac to inferior vena cava extended to suprahepatic veins (Figure 1), including upper mesenteric vein and splenic vein (Figure 2).

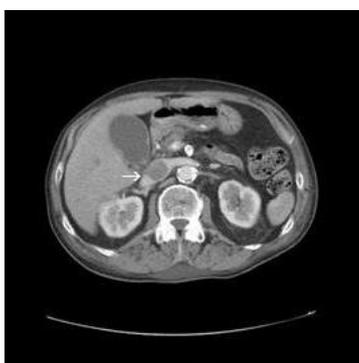


Figure 1. Arterial phase showing the inferior vena cava thrombosis (white arrow)



Figure 2. Portal phase showing the thrombosis of splenic vein and inferior vena cava (white arrow)

Immediately after diagnosis of massive thrombosis, therapeutic doses of endovenous sodium heparin were started. The implantation of a cava vein filter was considered but not available at that moment. The patient remained hemodynamically stable but signs of peripheral arterial compromise progressed. Both legs turned blue distally, from knees to both feet, and peripheral arterial pulses remained not palpable. Two days later the patient suffered sudden severe dyspnoea leading him finally to death.

Discussion

Thrombotic disorders in cancer patients include arterial thrombosis, venous thrombosis, migratory thrombophlebitis, nonbacterial thrombotic endocarditis and systemic paraneoplastic syndromes, such as thrombotic microangiopathy and disseminated intravascular coagulation. The mortality rate of proximal deep vein thrombosis is higher than that of distal deep vein thrombosis (1). The most common of all the above conditions is venous thromboembolism, which includes deep vein thrombosis and pulmonary thromboembolism. Both represent important clinical entities because of its high frequency, morbidity and mortality rates. Indeed, mortality of deep venous thrombosis is estimated to be 8 times higher in cancer versus non-cancer patients and it is associated with increased frequency of recurrences and bleeding complications (2). A variety of paraneoplastic thromboembolic disorders, confined to veins, arteries, or both, have been described and termed Trousseau's syndrome (3). In 1865, Trousseau was the first to report an increased incidence of venous thrombosis in patients with cancer. The venous thrombosis often was migratory, and the cancer was occult and difficult to diagnose (4). An accelerated course of peripheral vascular and ischemic heart disease has been reported in association with Trousseau's syndrome. Besides, thrombotic episodes may precede the diagnosis of cancer by months or years, and thus representing a potential marker for unknown and occult malignancy (5-10).

Besides, a variety of cancer-associated vasculopathies have been described, some sharing the paraneoplastic features associated with classic Trousseau's syndrome. Paraneoplastic vasculopathies are those cancer-associated vascular syndromes that occur at a distance from the primary tumor or metastases and are induced by the cancer through hormones, immunoglobulins, or other humoral mediators. The recognition of paraneoplastic disorders has a crucial

clinical importance because their appearance may be the first indication of malignancy (Table 1).

Deep venous thrombosis is by far the most frequent thromboembolic complication of cancer. The diagnosis is often difficult; enlarged pelvic lymph nodes may cause extrinsic compression of large veins with subsequent swelling of an extremity. This situation cannot be distinguished on clinical examination from

intrinsic occlusion of a vein (11-13).

Hepatic vein thrombosis and portal vein thrombosis are most often seen in patients with myeloproliferative disorders, lymphoma or colorectal adenocarcinoma. Portal hypertension and variceal hemorrhage may be the presenting symptom. Splanchnic vein thrombosis is an often unsuspected complication of cancer (13).

Table 1. Vascular syndromes associated with cancer

a.	Superficial thrombophlebitis, often migratory
b.	Deep venous thrombosis with possible embolization to pulmonary or systemic circulation
c.	Arterial thrombosis
d.	Arterial and venous thromboembolism
e.	Nonbacterial thrombotic endocarditis with possible embolization to systemic or pulmonary circulation.
f.	Cardiac thrombosis
g.	Accelerated course of peripheral vascular or ischemic heart disease
h.	Paraneoplastic vasculitis: Leukocytoclastic vasculitis Raynaud s phenomenon

Acute disseminated intravascular coagulation manifesting as widespread thrombotic, bleeding lesions and a severe consumptive deficiency of platelets and clotting proteins is rare in cancer patients in general, but common in patients with acute promyelocytic leukemia. In the latter, the disorder may even intensify when chemotherapy is administered (14).

The cancer-associated claudication is characterized by a more expedited course. Usually a rapid progression of ischemia exists with a high incidence of graft occlusion requiring vascular surgery for limb salvage. Principally, final relief of claudication depends specifically on the efficiency of cancer therapy (14). Besides, it has been demonstrated an increase in coronary instability in patients with cancer in the 2-year-period before cancer diagnosis compared with control subjects. Patients with colorectal cancer had the highest indices in the 2 years preceding cancer diagnosis. The lowest indices were recorded in those with prostatic and bladder cancer. Other possible etiologic factors, particularly the known coronary risk factors and anemia, were not statistically related to an increased risk of coronary events in the 2-year-period prior to cancer diagnosis (14-15). Furthermore, in a retrospective study, the rate of coronary events increased 40 times in the 2-year-period before the diagnosis of colorectal cancer and to lesser degrees in other malignancies; in the same patient population, there were only a few instances of stroke, accelerated peripheral vascular disease, and venous thrombosis, but no instance of vasculitis (17).

The antithrombotic treatment recommendations of deep venous thrombosis do not differ from non-cancer patients. The main objectives include anticoagulation,

medical stabilization of patient, the relief of symptoms, the resolution of the vascular obstruction and the prevention of complications and recurrences. A minority of patients will need other types of treatment such as thrombolysis or placement of vena cava filter (17).

Reviewing retrospectively our case, the syndrome of Trousseau presented as expression of a paraneoplastic syndrome secondary to a late stage of colonic adenocarcinoma. Although there were no signs of local or distant recurrence of the tumor, it is known that the hypercoagulability status and the secondary changes of the endothelium of vessels (arteries and veins) found in these patients increase the risk of arterial and venous thrombosis, even following adequate treatment.

References

- Galanaud JP, Sevestre-Pietri MA, Bosson JL, Laroche JP, Righini M, Brisot D, et al. Comparative study on risk factors and early outcome of symptomatic distal versus proximal deep vein thrombosis: results from the OPTIMEV study. *Thromb Haemost* 2009;102:493-500.
- Pérez G, Rodríguez AM, Ballesteros M, Infante ME, Inigo B. Enfermedad tromboembólica en el paciente oncológico. La enfermedad tromboembólica venosa (ETV) en el paciente médico. Madrid: THink-In Pharma Services, S. L, 2011:140-71.
- Goldsmith GH Jr. Hemostatic disorders associated with neoplasia. Forbes CD, Ratnoff OD, editors. *Disorders of hemostasis*. Philadelphia: Grune & Stratton, 1984:351-66.
- Trousseau A. Phlegmasia alba dolens. *Clinique Medicale de l'Hotel-Dieu de Paris*. London: New Sydenham Society, 1865:695 -727.

Trousseau's syndrome mimicking peripheral arterial disease

5. Edwards EA. Migratory thrombophlebitis associated with carcinoma. *N Engl J Med* 1947;240:1031-4.
6. Lieberman JS, Borrero J, Urrdeaneta E, Wright IS. Thrombophlebitis and cancer. *JAMA* 1961;177:542-5.
7. Nussbacher J. Migratory venous thrombosis of legs. *N Y State J Med* 1964;642:166-73.
8. Gore JM, Appelbaum JS, Greene HL, Dexter L, Dalen JE. Occult cancer in patients with deep venous thrombosis. *Arch Intern Med* 1987;147:556-60.
9. Goldberg RJ, Seneff M, Gore JM, Anderson FA Jr, Greene HL, Wheeler HB, et al. Occult malignant neoplasm in patients with deep venous thrombosis. *Arch Intern Med* 1987;147:251-3.
10. Griffin MR, Stanson AW, Brown ML. Deep venous thrombosis and pulmonary embolism: risk of subsequent malignant neoplasia. *Arch Intern Med* 1987;147:1907-11.
11. Naschitz JE, Yeshurun D, Gaitini D. Deep venous leg thrombosis and its differential diagnosis: the case for B-mode ultrasonography. *Int J Angiology* 1993;1:218-24.
12. Chaikoff EL, Campbell BE, Smith RB 3d. Paradoxical embolism and acute arterial occlusion: rare or unsuspected? *J Vasc Surg* 1994;20:377-84.
13. Sierra-Montenegro E, Sierra-Luzuriaga G, Calle-Loffredo D, Rodríguez Quinde M. Rectal cancer and Trousseau syndrome. Case report. *Cir Cir* 2013;81:242-5.
14. Mezouar S, Mege D, Darbousset R, Farge D, Debourdeau P, Dignat-George F, et al. Involvement of platelet-derived microparticles in tumor progression and thrombosis. *Semin Oncol* 2014;41:346-58.
15. Naschitz JE, Schechter L, Chang JB. Intermittent claudication associated with cancer-case studies. *Angiology* 1987;9:696-704.
16. Naschitz J, Yeshurun D, Abrahamson J, Eldar S, Chouri H, Kedar S, et al. Ischemic heart disease precipitated by occult cancer. *Concer* 1992;69:2712-20.
17. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e419S-e496S.