Angiology: Open Access
ISSN: 2329-9495

Barbalho et al., Angiol Open Access 2015, 3:1
DOI: 10.4172/2329-9495.1000141

Case Report Open Access

Superficial Thrombophlebitis Associated To Hepatocarcinoma: An Exuberant Manifestation

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Rec date: February 23, 2015; **Acc date:** March 18, 2015; **Pub date:** March 26, 2015

Abstract

The authors present a case of an elderly female with thrombophlebitis that led to the search for malignancy. A hepatocarcinoma was found, thus permitting its early diagnosis and probably the beginning of therapy long before it would present any symptom. Thrombophlebitis may represent an alert to an internal neoplasia, being considered a paraneoplasia, and all physicians must be acquainted with this association.

Keywords: Thrombophlebitis; Hepatocarcinoma; Cryoglobulin; Paraneoplasia

Introduction

Thrombophlebitis is characterized by the presence of thrombus in the venous lumen accompanied by inflammation of the vessel wall and surrounding tissues. The thrombotic state may be triggered by various genetic or acquired factors and may represent an alert signal to underlying malignancy.

The authors report the exuberant case of an elderly female patient, with a thrombophlebitis picture associated with hepatocarcinoma.

Case Report

A white, 77 years-old female patient, carrier of hepatitis C associated with Child's A6 liver cirrhosis, was admitted at the in-patient General Clinic of the University Hospital of the Federal University of Rio de Janeiro, Brazil. The patient was previously diagnosed with cryoglobulinemia. She presented dyspnea and daily fever of 38.5°C for a week, associated with emergence of erythematous-infiltrated lesion with local temperature increase in the left thigh. During the evolution, an abrupt appearance of new lesions occurred, some of which become ulcerated. There was no response to amoxicillin-sulbactam for 2 days followed by 7 days of cefazolin. The dermatologist´s opinion was then requested.

At the dermatological examination, erythematous and nodular lesions were observed. Some were ulcerated, necrotic, with about 2 cm in diameter in arciform shape. These lesions were located in the middle third of the anterior left thigh (Figure 1). There was asymmetric edema of lower limbs, more exuberant on the left side.

Diagnostic hypotheses for atypical mycobacteriosis, panniculitis and thrombophlebitis were raised. During the skin biopsy procedure, it was possible to observe a large thrombosed vessel in the topography of ulcerated nodules (Figure 2), supporting the hypothesis of thrombophlebitis. This was confirmed by blood analysis showing absence of deficiencies of C and S protein, factor VIII and Leiden factor V, associated to the histopathologic analysis (Figure 3) and by Doppler ultrasonography of the superficial and deep venous system examined bilaterally until the popliteal territory. On the left leg, the exam of the deep veins showed signs of partially rechanneled thrombosis in the territory of common femoral vein, presence of blood flow responsive to Valsalva maneuver on the distal territory, and ectasia of the saphena magna with massive thrombus in its interior. On the right, the deep systems were examined bilaterally until the popliteal territory and there was no sign of thrombosis. The exam of the surface structures revealed edematous infiltration of the sucutaneous tissue on the left thigh, serpiginous anecoic structures, with hypercoic content inside, arranged at the path of saphena magna vein. Color Doppler study did not observe central vascularization. The aspect was compatible with thrombotic saphena magna vein. There was increased echogenicity of adipose tissue, adjacent to the previously described vein, which probably corresponds to inflammatory/infectious involvement.

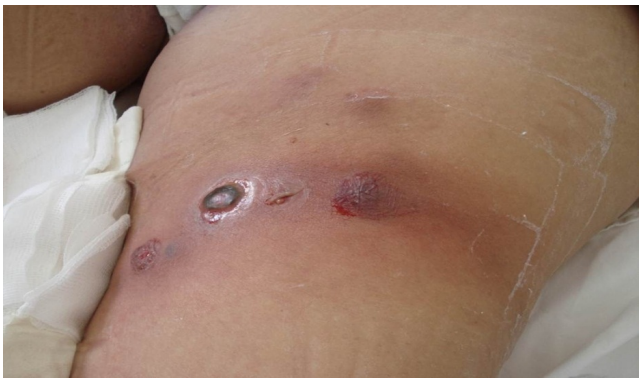

Figure 1: Erythematous-nodular lesions, some ulcerated, with necrosis in the middle of the anterior left thigh

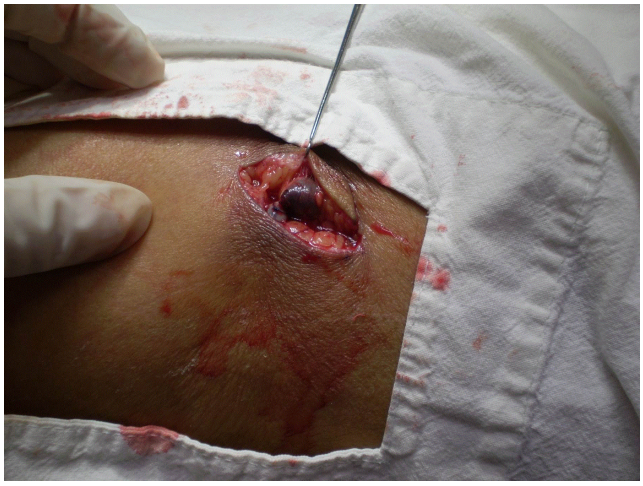

Figure 2: Large thrombotic vessel in the topography of the ulcerated nodules, observed during the skin biopsy

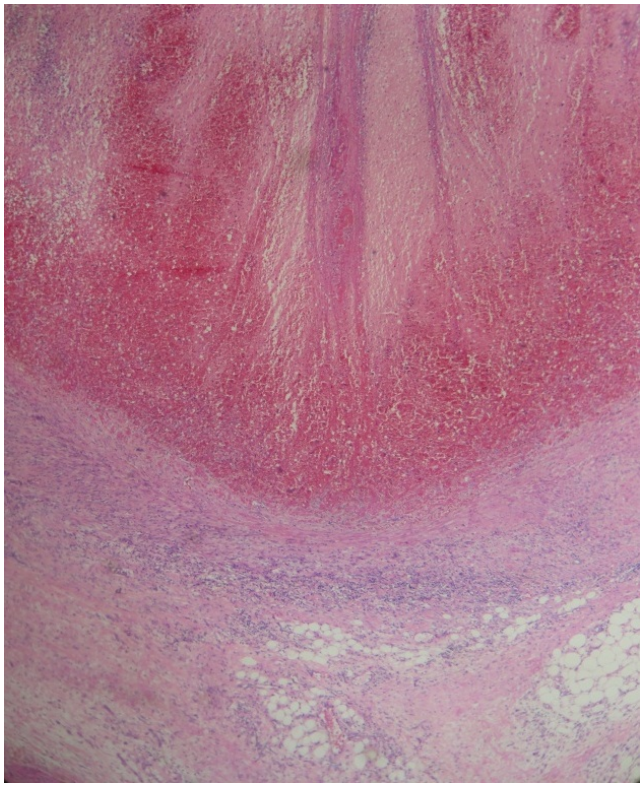

Figure 3: Venous wall surrounded by inflammatory cells with thrombus attached to the denuded intima (HE, ObjX 20)

The patient was treated at the medical clinic with full anticoagulation and was investigated for association with neoplasia. Computerized tomography of the abdomen showed an image suggestive of hepatocarcinoma associated to portal vein thrombosis (Figure 4).

The patient was submitted to anticoagulation and hepatic nodule percutaneous ethanol sclerotherapy. It was uneventful and she was followed in outpatient treatment with improving evolution of the skin lesions after 7 days of therapy.

Discussion

The increased predisposition to the occurrence of thromboembolic events is called thrombophilia. This can be triggered by numerous genetic or acquired factors [1-3]. Among these, the main causes are the antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative diseases, neoplasias, pregnancy and postpartum, nephrotic syndrome, hyperviscosity, use of oral contraceptives, drugs, trauma, surgeries and prolonged immobilization [4].

In this case, the presence of neoplasia and cryoglobulinemia, following the infection by hepatitis C virus, resulted in the installation of the thrombotic condition, although a causal relationship between the cryoglobulinemia and the thrombosis could not be proven.

Spontaneous appearance of venous thrombophlebitis was first described by Trousseau in 1865 and thus is known as Trousseau sign of malignancy [5]. Thromboembolic events occur in approximately 10 to 15% of patients with neoplasia, especially in the lung, pancreas, stomach, intestine, ovary, and prostate. They affect both the venous and the arterial area, and may occur before the onset of neoplasia or be its first sign, as observed in our patient. The mechanisms involved in the pathogenesis of thrombosis in malignant diseases have not yet been fully elucidated. Studies indicate that there is a probable formation of pro-coagulant substances by neoplastic cells. These substances would act as factor VII tissue activator or factor X activating protease. The detection of high levels of tumor necrosis factor (TNF) was also reported in 50% of patients with active neoplasia. TNF acts on the endothelial cells, facilitating the activation of coagulation and hindering fibrinolysis [4].

Cryoglobulins are immunoglobulins known for precipitating under low temperatures, below 37°C and re-solubilizing when reheated. They are called essential or idiopathic, if not associated with underlying diseases, and secondary, in the presence of neoplasia, autoimmune disease and infection. The association between mixed cryoglobulinemia and the hepatitis C virus infection was first reported by Pascual et al. in 1990, and occurs due to persistent stimulation of the immune system by the virus, which is lymphotropic [6].

This association is often observed and has been confirmed by various studies [7-9].

Brouet [10] classified cryoglobulins into types I, II and III according to the cryoprecipitate composition. Type I is monoclonal and with higher frequency of IgM or IgG classes, although IgA and Bence Jones cryoglobulins have already been described, and generally associated with lymphoproliferative disorders, such as lymphoma, myeloma, and Waldenstrom's macroglobulinemia. Types II and III are polyclonal immunoglobulins with a monoclonal component (type II), or without it, (type III).

Type II and III cryoglobulins are called mixed and are found in immune-lympho proliferative diseases, chronic inflammation, autoimmune diseases, chronic and acute infectious diseases [7,8]. In mixed forms, the clinical manifestations occur by deposition of immune complexes and subsequent activation of the classical pathway, which may lead to the development of pigmentary changes, petechiae,

distal necrosis, telangiectasia, urticaria, livedo, tissue necrosis and ulcers in the lower limbs [11,12]. It is worth to remind that Virchow's triad, characterized by endothelial lesion, stasis or blood flow turbulence and blood hypercoagulability, is the main factor that influences the formation of thrombi, the former being the most important [4].

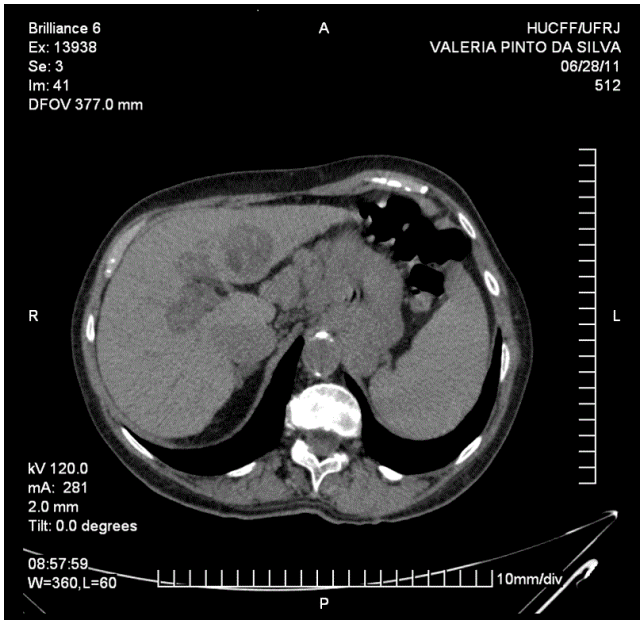

Figure 4: Abdominal computerized tomography showing image suggestive of hepatocarcinoma associated to portal vein thrombosis

Clinically, thrombophlebitis, when located in the saphenous vein or its superficial branches is characterized by erythematous nodular painful lesions and may be presented in chain throughout the venous pathway associated with temperature increase; a picture that can resemble cellulite, making it difficult to distinguish from an infectious process [13]. There is no lymphadenitis or peripheral edema, unless there is a deep underlying vein thrombosis [14]. Association with varicose veins or states of hypercoagulability are common, but may also be a warning sign for underlying malignancy, occurring especially in the apparently normal superficial vein [15], which was evidenced in our patient. As to the form not associated with varicose veins, it may be a consequence of intravenous injection or intravenous catheter insertion and if recurrent or disseminated, hypercoagulable states or neoplasms should be sought [14].

In the case presented, at the time of biopsy of the ulcerated skin lesion, a large thrombosed vessel was observed, which made us consider paraneoplasia. After screening, abdominal CT scan revealed hepatocarcinoma.

Conclusion

The facts presented in this report strengthen the possibility of thrombophlebitis representing an alert for an underlying malignancy, with all physicians being aware to consider its diagnosis, as well as guiding the search for eventual underlying disease, favoring an early diagnosis that can frequently provide a better prognosis for the patient.

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