

Atypical Site of Venous Thrombosis Despite Appropriate Anticoagulation in a Patient with Myeloproliferative Neoplasm

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ABSTRACT

The following case report and literature review will emphasize the individualized therapeutic management of a complex prothrombotic pathology. The onset of acute portal vein thrombosis in a patient with atrial fibrillation and good compliance to anticoagulation with a direct oral anticoagulant, who associates significant thrombocytosis, after excluding predisposing inflammations, infections or solid neoplasia, raises the diagnostic suspicion of myeloproliferative disorder, and imposes a complex interdisciplinary approach.

Keywords: portal vein thrombosis, myeloproliferative disorder, anticoagulation.

INTRODUCTION

Prothrombotic status in myeloproliferative neoplasm is multifactorial, comprising of a proadhesive and procoagulant endothelium, leukocytosis, procoagulant cell phenotype, and hyperviscosity (1). The onset of an acute venous thrombotic event, despite anticoagulation therapy with a direct oral anticoagulant (DOAC), in a

patient with good medication compliance can have a heterogenous etiology and imposes identification of prothrombotic local and systemic risk factors. □

CASE REPORT

We present the case of an 84-year-old underweight [body mass index (BMI) 17,45 kg/m²] female patient, admitted to the

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University Emergency Hospital of Bucharest, Romania, with complaints of incessant episodes of intense, diffuse abdominal pain in the last two weeks, aggravated progressively, and dyspnea in the last three days prior to admission.

Past medical history includes advanced chronic heart failure (III NYHA class), with preserved left ventricle ejection fraction (LVEF) of 55%, degenerative aortic valve disease with severe stenosis and moderate valve insufficiency, moderate mitral valve insufficiency, and permanent atrial fibrillation. The patient confirmed compliance with prescribed medications: beta-blocker, loop diuretic, and apixaban, with dose adjustment [2.5 mg twice a day (b.i.d.)]. She denied chest pain, dyspnea, syncope, upper and lower gastrointestinal bleeding, rash, neurological symptoms, and recent surgery. At admission, the clinical examination revealed compensated chronic heart failure, low grade fever (37.8°C), dyspnea with tachypnea, blood oxygen saturation level on breathing air of 98%, blood pressure of 100/60 mmHg, heart rate of 95 bpm, irregular, holosystolic murmur in the aortic area, radiating to both carotid arteries, and diminished peripheral pulses. The abdomen was distended but compressible on palpation, with normal breathing movements of the abdominal wall, and splenomegaly. No signs of peritoneal irritation and hepatomegaly were identified.

Laboratory tests indicated leukocytosis (22 000/uL), with important basophilia (12%), no anemia, significant thrombocytosis (1 000 000/uL), raised inflammatory markers, negative cardiac markers, a slightly increased level of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) of 250 pg/mL, elevated D-dimer levels ($>5.00 \mu\text{g/mL}$), mild hepatic cytolysis (aspartate aminotransferase 70 U/L and alanine aminotransferase 75 U/L), creatinine clearance 47 mL/min, without any electrolyte disturbance, and a normal urinalysis. The electrocardiogram revealed atrial fibrillation with a ventricular rate response of 96 bpm, without other pathological changes. Blood cultures were evaluated, being negative at 48 hours post-admission.

Echocardiography excluded infective endocarditis. Chest radiograph did not identify significant changes. Abdominal echocardiography findings were normal except mild splenomegaly. Thoracic computer tomography (CT) excluded

pulmonary embolism, solid neoplasia, and pulmonary infection. Abdominal CT revealed portal vein and left portal branch thrombosis, with patent superior mesenteric vein, hepatic perfusion disorders, and splenic infarcts, without signs of inflammation, infection or intra-abdominal neoplasia (Figure 1). Taking into account the clinical and paraclinical context of acute portal vein thrombosis atypical site in a patient under anticoagulation therapy, with significant non-reactive thrombocytosis and without local prothrombotic predisposing factors, the suspicion of myeloproliferative disorder was raised. By medullary biopsy and a positive result for Janus Kinase 2 (JAK2), hematological evaluation established the diagnosis of essential thrombocythemia.

Based on interdisciplinary (cardiology and hematology) evaluation, DOAC was replaced with low molecular weight heparin (LMWH) – dalteparin (0.4 mL subcutaneous injection b.i.d.), and cytoreductive therapy (hydroxyurea –500 mg tablet b.i.d) during hospitalization and for the first six months after discharge.

After six months, abdominal CT revealed recanalization of the portal vein trunk, persistence of hepatic perfusion disorders and splenic infarcts (Figure 2), and no intestinal ischemia compli-

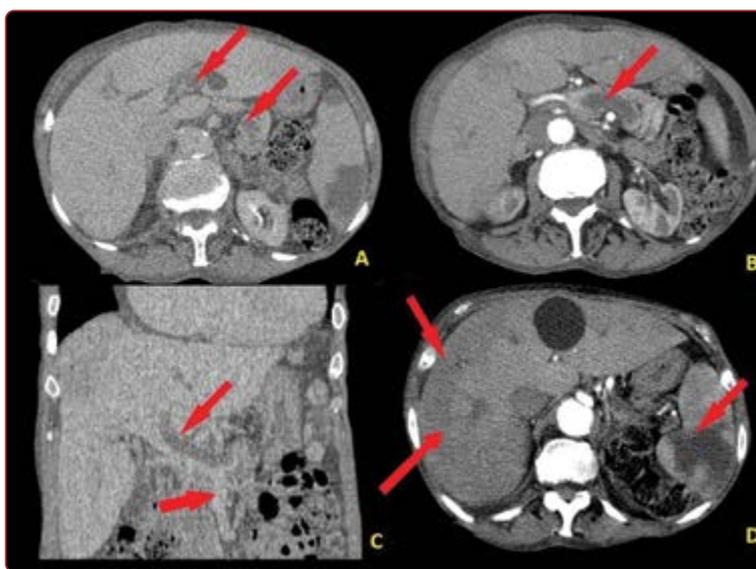


FIGURE 1. Abdominal computer tomography identifies (red arrows) thrombosis of portal vein trunk and left portal branch (A, B); patent superior mesenteric vein (C); and hepatic perfusion disorders and splenic infarcts (D)

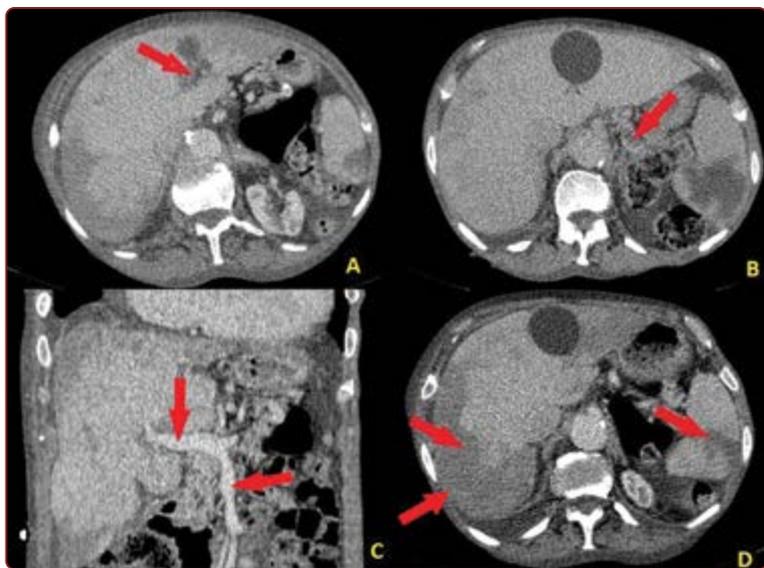


FIGURE 2. Six months follow-up abdominal computer tomography reveals (red arrows) recanalization of portal vein trunk (A, B); patent mesenteric vein (C); and persistent hepatic perfusion disorders and splenic infarcts (D)

cations caused by a potential extension of the thrombosis in the mesenteric veins.

Long term anticoagulation therapy was an absolute indication in the patient with atrial fibrillation and CHADS-VASC score of four points (HAS-BLED two points), acute portal vein thrombosis and essential thrombocythemia. At six months after discharge, the patient complained of multiple diffuse bruises at subcutaneous injection sites. There were concerns regarding the compliance of an underweight, frail, elderly patient with the LMWH therapy, and consequently we took into consideration switching to an oral anticoagulant.

Considering the current recommendations of the guideline for deep vein thrombosis and pulmonary embolism, we opted for switching parenteral anticoagulation to DOAC therapy – rivaroxaban, 15 mg per day. □

DISCUSSIONS

This clinical case emphasizes the importance of an accurate diagnosis of myeloproliferative neoplasm in patients with atypical sites of venous thrombosis (VT) and the challenging interdisciplinary management and optimal therapy in this complex prothrombotic pathology.

The incidence of thromboembolic events in patients with myeloproliferative neoplasms is

3-5% annually, while 40% of abdominal thrombotic events appear in patients with manifest or latent myeloproliferative disease (2). Essential thrombocythemia is a clonal autonomous thrombocytosis, included in the group of myeloproliferative neoplasms (3). The major criteria for essential thrombocythemia are thrombocytosis ($> 450 \times 10^9/L$), bone marrow biopsy showing proliferation of abnormal cells of the megakaryocyte lineage, presence of gene mutations [JAK2, calreticulin (CALR), myeloproliferative leukemia (MPL)], and not meeting criteria for other myeloproliferative neoplasms (3).

In cancer patients with venous thrombosis, current guidelines recommend edoxaban and rivaroxaban as DOAC alternative to LMWH (4). Moreover, Agnelli *et al.* demonstrated that apixaban is non-inferior to dalteparin in cancer-associated venous thromboembolism, without increasing the risk of major bleeding (5).

Venous thrombosis with atypical sites requires anticoagulation therapy (6). There are no randomized clinical trials confirming the efficacy and safety of DOAC in VT of unusual locations. Nevertheless, considering the scarce of cases of rare thrombosis, DOAC administration remains a controversial subject, and is based only on small observational studies and expert opinion (7, 8).

In patients with portal vein thrombosis, with or without cirrhosis, Priyanka *et al.* showed that DOAC could be an adequate alternative to conventional treatment with LMWH and VKA (7). More than that, Janczak *et al.* demonstrated the efficacy and safety of rivaroxaban and apixaban treatment in VT of atypical locations. The prospective study compared the rate of recurrence and bleeding between patients with VT of atypical site, who received treatment with DOAC, and two control groups, one comprising patients with VT of typical locations treated with DOAC and the other one comprising patients with atypical site VT receiving LMWH (8). Of all 36 patients enrolled in the study, there was a sizable percentage of subjects with cancer presenting with atypical venous thrombotic event location and treated with DOAC (52.8%), or receiving LMWH (95.7%) (8). The study revealed that rivaroxaban and apixaban in patients with VT of atypical site had comparable

efficacy and safety as DOAC in VT of common location, and similar outcomes to LMWH (8).

In our case, the development of uncommon site of VT in a patient with atrial fibrillation and associated comorbidities, with proper adherence to previous oral anticoagulation therapy, revealed a myeloproliferative disorder. The use of LMWH, even for a short period, in an elderly and frail patient diagnosed with hematological neoplasia reduced therapeutical compliance and altered the quality of life. Thus, by an interdisciplinary approach, even if there were no firm guideline recommendations, replacement of heparin with DOAC was mandatory, with favorable clinical evolution and excellent compliance. □

myeloproliferative disease, increasing morbidity and mortality. A multidisciplinary approach and personalized therapeutic strategy, based on patient's comorbidities and compliance to anticoagulation, become mandatory.

Although there is no strong evidence for the routine use of DOAC in atypical venous thrombosis in hematological cancers, selected patients can benefit from their use through good therapeutic efficacy and undoubted compliance. Data derived from future large randomized trials is of major interest for establishing recommendations for clinical practice in this special category of frail patients. □

CONCLUSIONS

Atypical localization of venous thrombosis can be the first clinical manifestation of a latent

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