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THROMBEMBOLIC EVENTS - A PREDICTIVE FACTOR IN PRIMARY MYELOFIBROSIS. A CASE REPORT AND A SHORT REVIEW OF THE LITERATURE

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ABSTRACT

Primary myelofibrosis is a myeloproliferative neoplasm associated with a progressive fibrosis of the bone marrow, which results in insufficient hematopoiesis and is characterized by a low survival rate. It may be frequently associated with a thrombembolic event, and the latter may precede the diagnosis of myelofibrosis. The concomitant treatment of these two nosological entities is a challenge as it limits the use of drugs that can control long-term complications. We present the case of a 62-year-old patient with a history of pulmonary thrombembolism, who addressed the Emergency Department with the following accusations: inflammatory edema of the lower right limb, palpitations, dizziness, diaphoresis, dyspnea at regular efforts. Based on the clinical signs and objective examination, vascular ultrasonography, the diagnosis of deep vein thrombosis was established. Complete blood count and marked splenomegaly raised suspicion about the presence of a myeloproliferative disease. The bone marrow biopsy and identification of the JAK2V617F supported the diagnosis of primary myelofibrosis. Anticoagulant treatment was performed, but there were two recurrences of deep vein thrombosis prior to the inclusion in the ruxolitinib treatment program. The aim of this paper is to emphasize the role of the predictive factor of thromboembolic events in myelofibrosis and the role of personalized therapy in the management of these patients. The report concluded that a complex therapy, personalized to each individual case, lead to improved prognosis of these patients.

Keywords: myelofibrosis, thromboembolism, personalized complex therapy, prognosis.

Introduction

In Europe, thromboembolic events: pulmonary thrombembolism (PE) and deep vein thrombosis (DVT) are a major health problem. Thus, 465,715 cases of DVT and 295,282 PE are estimated annually, and the number of deaths following them was 543,454 cases / year (1).

Risk factors involve endogenous factors: obesity, cancer, coagulation disorders, and exogenous factors such as hospitalizations and prolonged immobilization, trauma, repeated and large-scale surgery, age, pregnancy. The management is difficult because PE and DVT not only affect the quality of life of the patient but also the associate risks: recurrence (5-7% per year from the first episode), bleeding from anticoagulant treatment, death (2).

The post-thrombotic syndrome is one of the long-term complications of DVT, it is also called post-phlebitis syndrome and affects 23-60% of patients who have had a DVT event. Symptoms may include pain, paresthesia, edema, ulcers, skin hyperpigmentation in the affected limb. Susceptible to post-thrombotic syndrome are people who have a weight surplus, who have an age bigger than 65 years, or who have been given an inappropriate anticoagulant treatment, usually insufficient doses. The symptoms of DVT may persist for more than one month after

the diagnosis and a second event of DVT may occur to the same lower limb (3-7). In tumor diseases, venous thrombembolism (VTE) can occur in 4 - 20% of oncological patients at some stage. The incidence of VTE in the context of oncological diseases is 0.5%, compared to the general population, which constitutes 0.1% (8).

The definition of myelofibrosis includes clonal proliferation of myeloid cells associated with progressive bone marrow failure. In 2016, the World Health Organization, in the classification of myeloid neoplasms, specified the main diagnostic criteria: the presence of megakaryocytic proliferation and atypia; reticulin and / or grade 2 or 3 collagen fibrosis; failure to meet the criteria for essential thrombocythemia, chronic BCR-ABL1-positive myeloid leukemia, polycythemia vera, myelodysplastic syndrome and the presence of JAK2, CALR or MPL mutations. The minor diagnostic criteria are : leukocytosis, anemia, lactate dehydrogenas level above the normal limit, leukoerythroblastosis, palpable splenomegaly, criteria that need confirmation in two successive determinations (9).

Approximately 85% of patients with PMF have gene abnormalities such as: JAK2V617F, MPLW515 and calreticulin. Also, there can exist several mutations in epigenetic regulators and RNA splicing genes that coincide with driver mutations and perform essential roles in disorder evolution (10). The mutation in the Janus kinase 2 gene (JAK2) causes increased sensitivity of myeloid cells to cytokines and involves changing the valine by phenylalanine at position 617. Normally JAK2 provides instructions for creating a protein involved in cell proliferation. This protein participates in the JAK / STAT cell signaling a pathway and it drives chemical signals outside the cell to its nucleus. It also exercises control over the division of hematopoietic stem cells, responsible for the production of leukocytes, erythrocytes, platelets (11).

In primary myelofibrosis (PMF) up to 10% of patients may suffer from a thromboembolic event, and also have a risk of developing acute myeloid leukemia (12,13). Most thrombotic events occur at or in the two years before diagnosis (14).

Case presentation

We present the case of a 62-year-old man with myelofibrosis who expressed in writing his agreement for the processing of his medical data and participation in this study, carried out with the agreement of the ethics commission of the Dunarea de Jos University of Galati.

The patient, with a history of PE, 5 years ago, presents in the Emergency Department of the County Emergency Clinical Hospital Sf. Apostle Andrei Galati, for inflammatory edema to the right pelvic limb, local hyperthermia, palpitations, dyspnea at regular efforts, dizziness and diaphoresis. He was admitted to the Internal Medicine Department. The patient was tachycardic, and had prehypertension. The Computer tomography (CT) examination performed in the Emergency Department denied a possible PE. DVT of the lower right limb was confirmed by the Doppler ultrasound examination, and splenomegaly was also detected. The complete blood count (CBC) performed initially, indicated severe anemia, oxifil macrocytosis, normochromia, poikilocytosis and the presence of ovalocytes and dacryocytes. As CBC and DVT suggested a possible bone marrow impairment, the hematological examination was requested. Serum determination of vitamin B12, folic acid, and medullogram, osteo-medullary biopsy was indicated.

Investigations

CBC: Number of leukocytes- 3.10 x103 /μL (RR (reference range): 4-9x103 /μL), erythrocyte number - 2.73 μL (RR 5- 5.7 x 106 μL), hemoglobin - 8.0 g / dL (RR: 13-17 g / dL), haematocrit -29% (RR: 42-51%), mean corpuscular volume - 105.50 fL (RR: 80-95 Fl), mean corpuscular hemoglobin - 35.2 pg (RR: 25-34 pg), 2% metamyelocyte; platelets –174x103 / μL (RR: 150-450x103/μL).

Coagulogram: prolonged prothrombin time 22.20 s (RR: 11-13 s), international normalized ratio 2.05 (RR: 0.8 - 1.2), Prothrombin activity 38.15%(RR: 85%-100%), activated partial thromboplastin time 26s (RR: 21-35s), patient received anticoagulant treatment -

acenocoumarol.

Nonspecific inflammatory syndrome is present: erythrocyte sedimentation rate - 80 mm / h, (RR: 2-15 mm / h), fibrinogen - 713 mg / dL (RR: 200 - 400 mg / dL). C-reactive protein - 24 mg / dL (RR: <6 mg/ dL).

Doppler examination of the veins of the lower right limb: incompressible right popliteal vein with absent flow, increased lumen; posterior tibial vein incompressible, increased lumen with absent flow. An abdominal ultrasound revealed a hepatic hyper-echogenicity and the presence of a cyst formation of 8 mm diameter, left cortical renal cyst of 49 mm diameter, spleen with long axis 172 mm, splenic vein 10 mm. Electrocardiogram: sinus tachycardia, without other changes.

Uric acid 6.97 mg / dL (RR: 3.4- 6.7 md / dl), lactate dehydrogenase 658 U / L (RR: 240 - 480 U / L), folic acid 3.45 ng / mL (RR: 140-628 ng/Ml), vitamin B12 404 pg / Ml (RR: 180 - 914 pg / mL), hepatitis B surface antigen and hepatitis C antibody negative, molecular biology assays JAK2 homozygous positive, breakpoint cluster region-abelson fusion oncogene negative.

Microscopically the bone marrow was relatively normoblastic. The percentage marrow formula was: 83% granulocyte series (RR: 50 – 70%), 7% lymphocyte series (RR: 10-16%), 10% erythrocyte series (RR: 25-30%) and 0.5% thrombocyte series (RR: 0.2 - 0.5%). Granulocyte series was slightly stimulated, with the presence of all maturation stages, slightly hypergranular and inhibited in maturation; number of myeloblasts was 1%. The erythrocyte series was evidently inhibited, without dysplastic changes, with rare intermediate megaloblasts. Thrombocyte series was stimulated without an increased number of megakaryocytes, with nests of 35-40 normal platelets. No metastatic cells was detected.

Differential Diagnostic

Taking into account the history of PE, the current clinical signs and the patient's symptoms, the diagnosis of DVT of the right lower limb, the subsequent care was confirmed by the Doppler examination, not for problems. However, the identification of the bone marrow disease requires further investigations. Initial clinical and the laboratory data suggested a deficiency anemia of folic acid, insufficiency of bone marrow (myelodysplastic syndrome). Later, based on the medullograms, and an osteo-medullary biopsy, the diagnosis of MF is established according to the classification of myeloid neoplasms and acute leukemias by the World Health Organization: megakaryocytic proliferation and atypia, presence of JAK2, CALR, MPL mutation or presence of another clonal marker, palpable splenomegaly, lactate dehydrogenase above the maximum limit of institutions reference values, absence of essential thrombocytopenia, polycythemia vera, myelodysplastic syndromes, chronic myeloid leukemia (9).

Treatment

The patient was monitored by a hematologist, and he was included in the treatment program with ruxolitinib for constitutional symptoms .The complex, personalized patient therapy included various treatments: first of all it was started the anticoagulant therapy with low-molecular-weight heparin, the pacient received Enoxaparin 0.6 ml twice a day. It was mandatory the early initiation of vitamin K-antagonists, aiming an international normalized ratio of 2.5 (range 2.0–3.0) for secondary antithrombotic prophylaxis.

Treatment of anemia included red blood cell transfusion and folic acid 5 mg twice a day .For the control of hypertension and sinus tachycardia it was administered candesartan 16 mg once a day and metoprolol 50 mg twice a day.

Outcome and Follow up

Prior to the initiation of the etiological treatment, the patient was hospitalized for DVT at the level of the right femoral vein, which was also improved with the administration of anticoagulants (determined by performing CT scan of the chest, abdomen, pelvic with contrast substance and significant relief of lower limb edema). During treatment with ruxolitinib the patient returned to the Hematology section with severe anemia and thrombocytopenia. Correction with erythrocyte concentrate, folic acid, and prednisone administration resulted in a favorable

evolution. No new thromboembolic events were identified during the treatment with ruxolitinib. According to the international dynamic system of scoring and prognosis in MF, DIPSS - plus, the patient falls from high risk, into the intermediate risk group - 2, with a score of 2, and a median survival estimated at 35 months.

Discussions

In the pathological context (MF), bone marrow fibrosis occurs, due to the polyclonal

reaction to cytokines, after which the growth factors are modified: β, vascular endothelial, epidermal, fibroblastic (15). However, only 50 - 60% of patients with primary MF have a JAK2 gene mutation, but the rest have a major mutation of the calreticulin (CALR) coding gene (16,17). CALR being a multifunctional protein, which participates in transcriptional regulation, prevents the export by the endoplasmic reticulum (RE) to the Golgi apparatus of misfolded proteins, and binds to antibodies in systemic lupus. The localization of this protein is considered to be predominantly in RE.

Currently the prognosis in MF is performed with the help of international dynamic system of scoring and prognosis in MF(IPSS, DIPSS, DIPSS – plus), which include age, blood count, need for red blood cell transfusion, circulating blasts, constitutional symptoms and karyotype analysis. In patients with MF with intermediate risk, the survival rate was 5 years, and in those with high risk, less than 2 years (18).

Despite the fact that the patient falls into the intermediate risk group - 2 according to DIPSS - plus, it should be noted that treatment with ruxolitinib could change the current prognosis towards a more favorable one. The COMFORT Trials I and II suggested a 30% reduction in the risk of death when using ruxolitinib, and the survival median was 5.3 years compared to 3.8 years in the control group (19). Long-term treatment between 48 and 60 months resulted in stabilization of bone marrow fibrosis, and reduction the size of the spleen and of the liver (20,21).

Although treatment with JAK2 inhibitors is promising from an etiological perspective, secondary MF anemia is a particular problem that needs to be resolved with additional efforts. Because ruxolitinib itself can cause haematological disorders with a frequency of 10% and above, of which 96.1% represent anemia, 69.8% thrombocytopenia and neutropenia up to 18.7% (22).

Clinical trials have shown decreases in levels of interleukin-6, C-reactive protein and tumor necrosis factor alpha during treatment with ruxolitinib (23). Clinical studies have also shown that ruxolitinib is able to reduce splenomegaly as well as symptoms and weight loss (24). Corticosteroids may be temporarily effective and should therefore be used in combination with other therapies. The use of erythropoiesis stimulants is only real when MF is with moderate anemia without transfusion need. Androgenic drugs are contraindicated in the association of MF with VTE (25).

Clinical studies have investigated the links between splenomegaly and the occurrence of thrombotic and thromboembolic events and have shown a correlation between decreased spleen size and reduced incidence of thromboembolic events in patients with MPN (26).

Morbidity and mortality of patients with MPN are significantly influenced by the occurrence of thrombic or thromboembolic events (27,28). Also, the history of thrombosis and the age of more than 60 years are strongly correlated with the occurrence of vascular complication (29,30). The study of 707 patients with PMF observed that the presence of the JAK2V617F mutation and the age over 60 significantly anticipates thrombosis (12).

In these patients, after VTE, the rate of repetitive thrombosis is 6.0 to 6.5 per 100 patient-years. Also, chronic treatment with VKA is associated with a evident benefit, decreasing the incidence rate of recurrence from 48 to 69% as regards no treatment at all (31-34).

VTE events in MF tend to occur in unusual places such as splanchnic vein 20%, and cerebral venous sinus 6% (35).

The pathophysiological mechanism of thrombosis is not fully elucidated but includes: platelet activation, platelet adhesion to leukocytes, endothelial activation, initiation of coagulation cascade. Increased platelet activation, elevated P-selectin expression, platelet membrane

mutations, and alphagranule depletion were observed in patients with MF (36-38). It is hypothesized that abnormal membrane platelets that activate into leukocytes (forming complexes with monocytes) would be involved, and then vascular endothelium would be activated, which will induce the coagulation cascade (39).

In conclusion, in myeloproliferative neoplasms, major indicators of a initial venous thromboembolism are the history of VTE, inherited thrombophilia and older age. Also, the patients with JAK2 V617F mutation are more predisposed to venous thrombosis. The relationship between male sex and leukocytosis has been also described (31).

Antithrombotic treatment may create MF management difficulties, as it oscillates between increased risk of thrombosis and bleeding in the context of MF-associated thrombocytopenia.

We can also discuss a possible prothrombotic effect of the non-selective beta-blocker in the chronic therapy of hypertension of this patient considering the observations from clinical studies performed in patients with liver cirrhosis receiving therapy to prevent bleeding from esophageal varices with non-selective beta-blockers and develop more frequently, thrombosis of the portal vein compared to cirrhotic patients who do not receive this prophylactic therapy (40-42). Thus, in patients at risk of deep vein thrombosis, an antiarrhythmic other than beta-blocker may be considered for the treatment of tachyarrhythmia.

Conclusion

Myelofibrosis is a rare disease with a poor prognosis, personalized therapy of each case is essential to improve the patient's vital prognosis. Major causes of morbidity and mortality in patients with MPN are represented by arterial and venous thrombosis that requires antithrombotic treatment. Thromboembolism can be considered a predictive, personalized, revealing diagnostic factor.

Consent for Publication

Written informed consent was obtained from the next of kin of the patient for the publication of this report and any accompanying images.

Ethics Statement

Ethical approval for publication was obtained from ''Dunarea de Jos'' University Of Galati Ethics Commission (reference number: 295/25.03.2021)

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Not aplicable

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