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ESSENTIAL THROMBOCYTHEMIA AS A CAUSE OF SEVERE CHEST PAIN: CASE REPORT

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Summary

Essential thrombocythemia is a myeloproliferative disease that is characterized by elevated platelet count, specific changes of megakaryocyte lineage in bone marrow as well as non-specific clinical symptoms. This case report presents a 40-year-old female complaining of episodic chest pain and shortness of breath. Cardiologists ruled out cardiovascular pathologies after performing electrocardiography (ECG), echocardiography, a complete blood count, and a treadmill test. After a recurring episode of chest pain, the patient was sent to the emergency department on suspicion of acute coronary syndrome or pulmonary embolism but routine tests (ECG, troponin I, D-dimers, computed tomography pulmonary angiography) excluded these diagnoses. Essential thrombocythemia was diagnosed based on bone marrow trephine biopsy results and positive genetic testing for *JAK2* mutation. The patient was assigned to the low-risk group, therefore, she received aspirin therapy as well as correction of cardiovascular risk factors.

Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm, characterized by thrombocytosis, and is usually associated with one of three mutations in *JAK2, CALR,* and *MPL* genes [1]. On average, the annual incidence of ET is 2 (from 0.2 to 3, depending on the source) cases per 100 000 population [1, 2]. Females are approximately twice more likely to develop ET than males. While most patients are diagnosed at around 60 years old, one-fifth of them receive the diagnosis before the age of 41 [2]. The case report presents a 40-year-old female, who was complaining of chest pain and shortness of breath. In this clinical case report, we emphasize the importance of early diagnosis and prevention of possible complications. In addition to the case presentation, we also conducted a literature review regarding the latest knowledge about the management of ET.

The aim of this article is to present an unusual case of severe chest pain and to discuss the most recent literature about ET.

Case description

A 40-year-old Caucasian female presented with persistent crushing, squeezing chest pain that radiates to the jaw area and is related to physical exertion. The patient also experienced shortness of breath and heart palpitations. Such episodes usually lasted a few minutes and would resolve spontaneously; the total duration of these symptoms was one week. Medical history revealed that the patient had experienced multiple transient ischemic attacks three years ago. One of these attacks manifested as intense headaches, nausea, incoherent language, leg paralysis which lasted approximately 4 hours. During that time, an elevated platelet (PLT) count was discovered; however, no further investigation was performed. Initial blood tests showed hypercholesterolemia (lipid panel: total cholesterol 6.72 mmol/l, high-density lipoproteins 1.84 mmol/l, low-density lipoproteins 4.26 mmol/l, triglycerides 1.4 mmol/l) and thrombocytosis (PLT $572x10^9$/l), thus, the patient was referred to consultations of a hematologist and a cardiologist.

Clinical examination at the cardiologist showed no abnormalities. ECG revealed no signs of ischemia or arrhythmia. Repeated blood tests indicated dyslipidemia and increasing thrombocytosis (PLT $625x10^9$/l). Oral nitroglycerine was prescribed to reduce ischemic chest pain. On suspicion of unstable angina, the patient was referred to the Emergency Department for extensive evaluation. Laboratory tests showed normal serum troponin levels but an increase in D-dimers (1.21 mg/l, while the normal value is less than 0.5

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mg/l). The protocol for suspected pulmonary embolism management was carried out. Computed tomography pulmonary angiography revealed no signs of PE; therefore, this diagnosis was ruled out. Considering the stable condition of the patient and the lack of evidence to suggest an acute pathology, a decision was made to continue investigating in an outpatient setting. During repeated visits to the cardiologist, multiple tests were conducted. ECG and echocardiogram were normal, as well as the treadmill test; however, the hemodynamic reaction to the latter was not adequate, as the rise of arterial blood pressure did not correspond with physical exertion.

The patient was also consulted by the hematologist. Complete blood count, coagulation panel, and abdominal ultrasound were performed. The latter did not suggest any pathological enlargement or malignancy in either spleen or lymph nodes. The blood test showed increasing thrombocytosis (PLT 653x10^9/l). The myeloproliferative disorder was suspected, therefore, bone marrow trephine biopsy and genetic testing for *JAK2* gene mutation were recommended. The initial treatment plan included daily doses of Aspirin (75 mg) to reduce platelet aggregation. Histological analysis of bone marrow trephine biopsy revealed slightly increased cellularity in the bone marrow (70%), normal maturation and differentiation in erythropoiesis and granulopoiesis, a higher ratio of megakaryocytes with hypersegmented nuclei. These results allowed differentiating between ET and pre-primary myelofibrosis. Results of genetic test confirmed the *V617F* mutation of the *JAK2* gene. Hematologists were, therefore, able to specify the diagnosis as essential (hemorrhagic) thrombocythemia type 0 with low risk. The recommended treatment of daily anti-platelet medication (Aspirin 75-100 mg) was continued with hematologist supervision.

Discussion

Essential thrombocythemia is one of the eight neoplasms, classified as a myeloproliferative disease by the WHO [1]. ET is diagnosed based on WHO diagnostic criteria. Major criteria include:

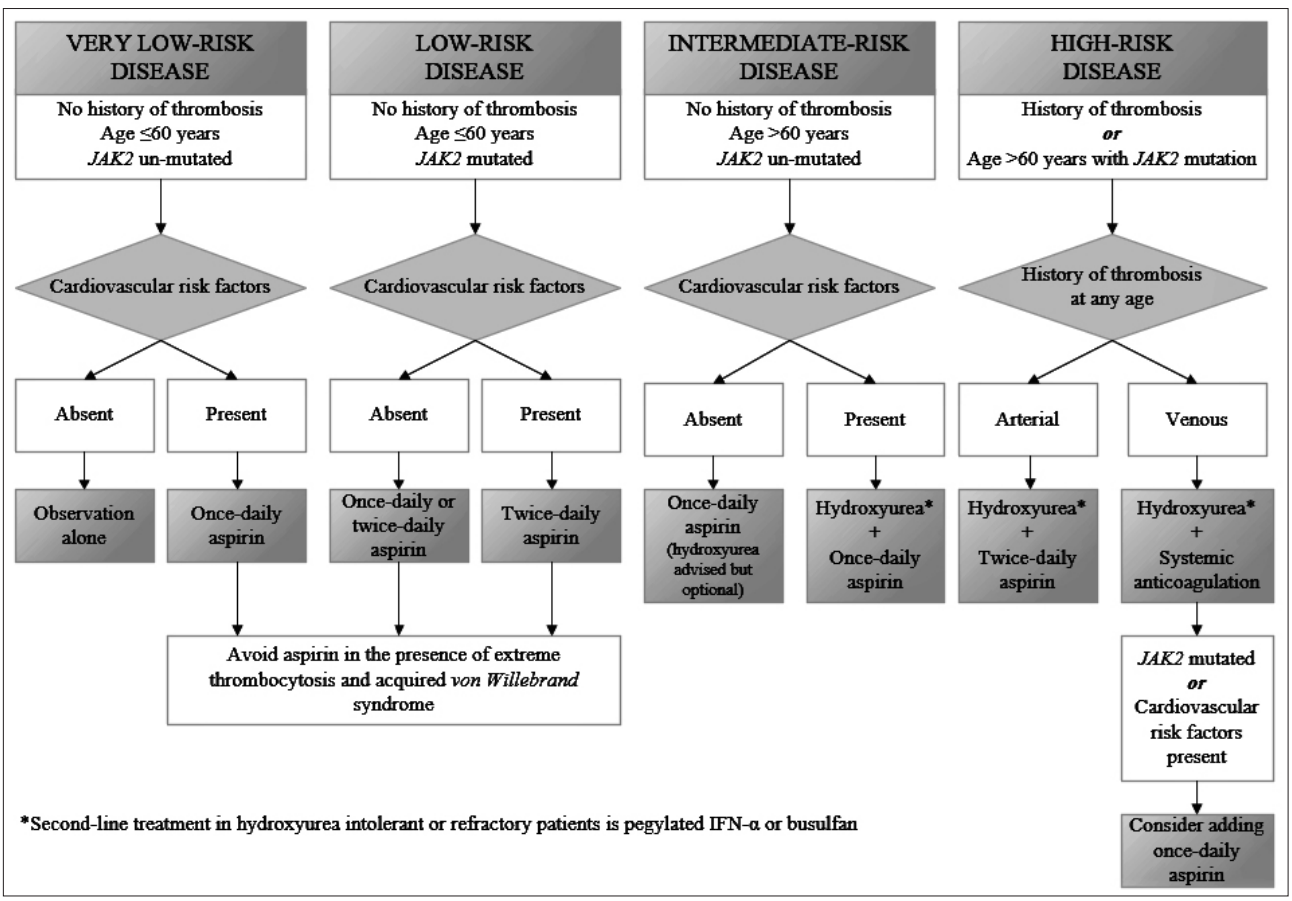

Figure 1. Algorithm for the treatment of essential thrombocythemia [8,10].
IFN-α – Interferon alpha, JAK2 – Janus Kinase 2 gene.

1. Elevated platelet count (> 450 000 per cubic millimeter).

2. Bone marrow megakaryocyte proliferation and loose clusters.

3. Not meeting WHO criteria for *BCR-ABL11CML*, polycythemia vera, primary myelofibrosis, myelodysplastic syndromes, or other myeloid neoplasms.

4. *JAK2 V617F, CALR,* or *MPL* mutation.

Minor criteria include presence of clonal marker or evidence of reactive thrombocytosis [1,2]. To confirm the diagnosis, the patient must meet all 4 major criteria or the first 3 and the minor criteria [4]. It is especially important to exclude any secondary causes of thrombocytosis as well as underlying myeloid cancer before confirming the diagnosis of ET [5]. Histopathology is the main tool to differentiate between the aforementioned diseases [4]. The histological pattern of ET includes normal or reduced cellularity, enlarged, mature megakaryocytes with hypersegmented nuclei [4].

The mutations that cause myeloproliferative neoplasms *(JAK2, MPL, CALR)* are usually sporadic; however, 7% of cases involve a familial predisposition [6]. It is important to determine the mutation because it might change the course of treatment. The most frequent mutation is *JAK2V617F* (Janus Kinase 2 gene mutation), which is found in 50-60% of all cases of ET [7]. The acquisition of *JAK2V617F* mutation can occur at any age but myeloproliferative neoplasms are quite rare before the age of 50 and tend to occur in females more commonly than males [6].

Most patients with ET do not experience any symptoms, although, a proportion of them present with thrombotic or hemorrhage complications [1,2]. Symptoms such as weight loss, splenomegaly, vasomotor symptoms, thrombosis at multiple or unusual sites could potentially indicate malignancy [5]. Perhaps the most common complications are stroke, transient ischemic attacks, deep vein thromboses, PE, peripheral artery occlusion, unstable angina or even myocardial infarction (MI) [1]. In our case, the patient described symptoms similar to PE or MI, thus, diagnostic protocols for these diseases were carried out. After successfully excluding any acute pathology, the cause of unusual chest pain and elevated PLT count was further investigated by hematologists.

Patients with ET have a slightly lower life expectancy than those without the disease [5,8]. The presence of *JAK2V617F* mutation is associated with a higher risk of thrombosis and a lower risk of post-ET myelofibrosis [9]. The main risk factors for overall survival in ET include advanced age, history of thrombosis, leukocytosis, anemia, and male sex [10]. Accordingly, patients with ET are stratified into four categories (Figure 1): very low-risk, low-risk, intermediate-risk, and high-risk [8,10].

Treatment is based on risk stratification groups (Figure 1) and the primary goal is to prevent cardiovascular events [5]. This includes modification and treatment of cardiovascular disease risk factors such as diabetes, hypertension, obesity, smoking, and hypercholesterolemia, as well as antiplatelet therapy [1]. Low-dose aspirin (40-100 mg/day) is recommended for all ET risk groups except the patients with very low-risk disease and no cardiovascular risk factors [1,8,10]. Recent studies have shown that aspirin therapy is beneficial in preventing arterial or venous thrombosis and also in alleviating vasomotor symptoms (e.g., headache, lightheadedness, tinnitus, atypical chest pain, paresthesias, erythromelalgia) [6,9]. In addition to low-dose aspirin, intermediate-risk patients with present cardiovascular risk factors and all patients with high-risk disease should receive cytoreductive therapy. The first-line and the only cytoreductive agent reducing the risk of thrombotic events is hydroxyurea, also known as hydroxycarbamide. The doses of this medication must be titrated to keep the platelet count normal [9]. Interferon-α (IFN-α) and busulfan can be chosen as second-line drugs if the patient is either intolerant or resistant to the aforementioned medications [1,7,8]. Our patient responded really well to aspirin therapy – chest pains did not reoccur, although, the PLT count remains slightly elevated.

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ESENCIALINĖ TROMBOCITEMIJA − SUNKAUS KRŪTINĖS SKAUSMO PRIEŽASTIS: KLINIKINIS ATVEJIS

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Raktažodžiai: esencialinė trombocitemija, trombocitozė, mieloproliferacinė liga, kaulų čiulpų trepanobiopsija.

Santrauka

Esencialinė trombocitemija yra mieloproliferacinė liga, apibūdinama padidėjusiu trombocitų skaičiumi, specifiniais megakariocitų pokyčiais kaulų čiulpuose ir nespecifiniais klinikiniais simptomais. Šiame straipsnyje pristatoma 40 metų pacientė, besiskundžianti epizodiniu krūtinės skausmu ir dusuliu. Užrašius elektrokardiogramą (EKG) ir atlikus širdies echokardiografiją, bendrą kraujo tyrimą ir bėgimo takelio testą, buvo atmesta širdies ir kraujagyslių patologija. Pasikartojus intensyviam krūtinės skausmui ir įtarus ūminį koronarinį sindromą ar plaučių emboliją, pacientė buvo siunčiama į skubiosios pagalbos skyrių tolesniam ištyrimui. Atlikus būtinus tyrimus (EKG, troponinas I, D-dimerai, KT angiografija) abi diagnozės buvo atmestos. Esencialinė trombocitemija diagnozuota remiantis kaulų čiulpų trepanobiopsijos rezultatais ir JAK2 mutacijos nustatymu. Pacientė priskirta mažos rizikos grupei, todėl paskirtas gydymas aspirinu bei širdies ir kraujagyslių rizikos veiksnių korekcija. Darbo tikslas – pristatyti klinikinį atvejį ir aptarti naujausius esencialinės trombocitemijos diagnostikos ir gydymo principus.

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