Scholars Journal of Medical Case Reports **ISSN 2347-6559 (Online)**
Sch J Med Case Rep 2014; 2(1):19-21 **ISSN 2347-9507 (Print)**

(An International Publisher for Academic and Scientific Resources) DOI: 10.36347/sjmcr.2014.v02i01.007

The Role of Inflammation in Essential Thrombocythemia Associated with Ischemic Heart Disease

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Abstract: It is accepted that in essential thrombocythemia there is an inflammatory status possibly responsible even for the disease appearance that predisposes to genomic instability (with possible new cancers) and promotes early appearance and progression of atherosclerosis with its various locations. We present the case of a female patient diagnosed at 46 years simultaneously with acute myocardial infarction, essential thrombocythemia and chronic hepatitis C. Her successive treatments (including pegylated interferon and ribavirin) and evolution are presented. The association of these diseases is discussed and the lack of achieving complete virologic response is explained.
Keywords: Chronic hepatitis C, Essential thrombocythemia, Hydroxycarbamide, Inflammation, Interferon-α, Ischemic heart disease

INTRODUCTION

The discovery of *JAK2 V617F* and *MPL* exon 10 mutations (*S505N W515L, W515K, W515A*) [1] represents a breakthrough in understanding the pathogenesis of Philadelphia-negative chronic myeloproliferative neoplasms, including essential thrombocythemia. But not all patients with essential thrombocythaemia have got any of the mentioned changes. Therefore, many researchers believe that these mutations are not the initiating factor in the process of malignant transformation. It was noted that many patients with chronic myeloproliferative neoplasms have both a chronic inflammatory process that may be involved in disease pathogenesis and favor the genomic instability with risk of new cancers. The same chronic inflammation contributes to the progression of atherosclerosis with its various locations and to coagulation activation responsible for prothrombotic status of these patients. We present the case of a female patient with chronic hepatitis C and essential thrombocythemia who has had an acute myocardial infarction.

CASE REPORT

The ethical committee permission to publish this onco-hematological case was obtained. A female patient aged 51 years had suffered four years and half ago a heart attack in Italy, for which she had undergone coronary artery bypass graft surgery. On that occasion it was found that she was infected with hepatitis C virus and she had thrombocytosis. Investigations that have been made revealed megakaryocytic hyperplasia of bone marrow and the presence of *JAK2 V617F* mutation in heterozygous variant. The treatment with hydroxycarbamide and aspirin (75 mg/day) was started which she continued until coming to Romania, 1 year after the diagnostic setting. In Romania she had normal transaminases but platelets were 835000/mm^3, for which she began anagrelide therapy in order to avoid the possible occurrence of a secondary cancer under hydroxycarbamide, but, in monotherapy, it was badly tolerated (she had chest pain suggestive for angina) and therefore the dose was reduced (1 mg/day) and hydroxycarbamide (1000 mg/day) was associated for 1 year and 2 months. Discontinuation of therapy with anagrelide for 4 months, when she went Romania, while she took only hydroxycarbamide, has increased the number of platelets (587000/mm^3), but she had no anginal crisis. At the request of the patient, she continued only with hydroxycarbamide, but in higher dose (1500 mg / day) for 3 months.

FibroMAX test showed a METAVIR score 2 for activity and 2 for fibrosis and HCV viremia level was 62903 UI/ml (4.80 log/ml), which supported the indication of treatment with pegylated interferon-α and ribavirin, which went instead hydroxycarbamide. Interferon-α therapy is indicated both for chronic hepatitis C as well as essential thrombocythemia, given that the patient had a thrombotic history. Pegylated interferon and ribavirin therapy was well tolerated, except for a mild leukopenia, but neutrophil polymorphonuclears did not decrease below 1700/mm^3 and did not require interferon dose reduction. After 4 weeks of treatment viremia was 548 UI/ml (2.77 log/ml) and after 12 weeks, hepatitis C virus RNA was undetectable (<15 UI/ml). She continued the treatment up to 48 weeks together with bezafibrate 2x200 mg/day (for hypertriglyceridemia associated, which widened during treatment and reached up to 965 mg/dl) and

rosuvastatin 10 mg/day (for its cardio-vascular pleiotropic effects), under which she was whithout liver cytolysis, serum triglyceride level was normalized (143 mg/dl) and total cholesterol remained normal, however, she had hypo-HDL cholesterol (34 mg/dl). Before the end of interferon therapy she presented the symptoms of a prepiloric gastric ulcer (a niche with a diameter of 1.5 cm), treated with esomeprazole. At the end of therapy with pegylated interferon and ribavirin (after the 48th week) viremia was positive (264941 UI/ml – 5.42 log/ml) without cytolysis and subsequently with serum levels at the upper limit of normal (alanine aminotransferase 39 U/L and aspartate aminotransferase 40 U/L). Platelet counts began to increase (604000/mm^3), which is why hydroxycarbamide therapy resumed, under which the platelet count was normalized (351000/mm^3) and she did not has liver cytolysis.

DISCUSSION

A patient with essential thrombocythemiawith 1300000 platelets/mm^3, also infected with hepatitis C virus, who had aortic insufficiency required thrombocytapheresis before cardiopulmonary bypass [2]. To our patient, who had lower values of platelets (less than 1 million/mm^3) bypass surgery was performed without thrombocytapheresis. It is known that at a value of platelets over 1500000/mm^3 essential thrombocythemia predisposes to bleeding [3], and at smaller values, but over those normal predispose to thrombosis. Also in the absence of essential thrombocythemia, any surgery intervention produces bleeding that can result in reactive thrombocytosis. To avoid the bleeding produced by the increased thrombocythosis in patients with essential thrombocythemia and for the surgery to be conducted in the safest conditions, prior thrombocytapheresis may be used in patients with high thrombocytosis, to which cytoreductive therapy has no time to act in situations of emergency. Thrombosis can be prevented by anticoagulant therapy.

Simultaneous discovery of chronic infection with hepatitis C virus and essential thrombocythemia do not exclude the possibility of intervention of chronic inflammation in the pathogenesis of essential thrombocythemia to the presented patient. In the literature there are opinions that the chronic inflammation is responsible for the increased oxidative stress in the bone marrow, which would induce mutations in hematopoietic cells; epigenetic alterations would be the trigger and driver of clonal evolution of essential thrombocythemia [4]. Besides *JAK2 V617F* mutation role, existing in presented patient in heterozygous variant, aberrant expression of miRNAs 10a and 150 may have pathogenetic role, according to the literature [5]. In addition, miR-433 negatively regulates stem cells proliferation and differentiation in studies made *ex vivo* [6]. Genomic instability induced inflammation may not only initiate clonal evolution, but also favor the evolution of essential thrombocythemia towards myelofibrosis [7].

But the association betwen essential thrombocythemia, ischemic heart disease and dyslipidemia may not be coincidental. Chronic inflammation often present in essential thrombocythemia, promotes premature atherosclerosis (patients underwent an acute myocardial infarction at only 46 years) [7]. Essential thrombocythemia is involved in the pathogenesis of acute coronary syndrome, by the predisposition to thrombosis.

Interferon and statins used for the treatment of the presented patient act against chronic inflammation in essential thrombocythemia [7] and infection with hepatitis C virus. In addition, interferon allows to control thrombocytosis. Statins may reduce the generation of thrombin (involved in the pathogenesis of liver fibrogenesis) and increase permeability and lysis of thrombus [8]. It is known that some statins added to the standard treatment of chronic hepatitis C with pegylated interferon and ribavirin help to improve early, rapid and sustained virologic response [9].

Why did the patient not achieve complete virologic response, despite this? It is known that hepatitis C virus activates STAT3 through oxidative stress and some cellular kinases, including JAK2; it is suggested that STAT3 may also be involved in the replication of hepatitis C virus RNA [10]. To the presented patient, *V617F* mutation realizes a continuous activation of *JAK2* gene, which contributes to continuous activation of STAT3, potentially excessive stimulating the replication of hepatitis C virus. Although complete virologic response was not achieved, pegylated interferon-α therapy helped reducing the rate of progression of liver fibrosis. Ideally, the patient should begin a triple combination therapy for the treatment of chronic hepatitis C or at least continue therapy with interferon-α for essential thrombocythemia, but these therapeutic modalities are not yet reimbursed by the National Health Insurance in Romania for these diseases.

Besides platelet count normalization, it is important that patients with essential thrombocythemia benefit from statin therapy (if tolerated) prevent or treat dyslipidemia, progression of atherosclerosis, commonly present to them, and reduce the thrombotic risk (through their vascular pleiotropic effects, decreased thrombin generation and intervention against thrombus).

CONCLUSION

Chronic inflammation of patients with essential thrombocythemia favors the early appearance of ischemic heart disease and *V617F* mutation is involved in the activation of hepatitis C virus replication. In addition, genomic instability present in

essential thrombocythemia (which will persist until the discovery of an effective medicine) predisposes the patients at the appearance of a new cancer.

Note: All authors contributed equally to drafting the article.

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