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A Rare Case of Thrombocytosis with Duble Malignant Etiology – Pathogenetic Interrelationships and Consequences

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Abstract: The etiological diagnosis of each thrombocytosis is a challenge for practitioners. There are situations where essential thrombocythemia is associated since the diagnosis, but sometimes also subsequently, with thrombocytosis evolving conditions. On the other hand, reactive thrombocytosis can be accompanied by essential thrombocythemia. We present the case of a patient who at diagnosis had colon cancer and essential thrombocythemia. Although essential thrombocythemia was treated according to guidelines, colon cancer relapsed and its evolution was unfavorable. The mechanisms that may explain the association of the two malignant proliferation and by which essential thrombocythemia may contribute to relapse and unfavorable evolution of colon cancer are discussed.
Keywords: Colon cancer, Essential thrombocythemia, Genomic instability, Hydroxycarbamide, Interferon, *JAK2V617F*, Second cancer, Statin, Thrombocytosis, Thrombosis.

INTRODUCTION

The diagnosis of essential thrombocythemia (ET) implies the exclusion of all causes of reactive thrombocytosis. There are also cases of ET which coexist at diagnosis with one or more conditions that evolve with reactive thrombocytosis. This issue is very important for medical practice. On the other hand, clinicians should also be aware to rule out a possible ET associated to different causes of reactive thrombocytosis. Finding a cause of reactive thrombocythosis is not a reason to exclude a possibly associated ET. We have to prove every time that the possible haematological malignancy is excluded. In addition, ET must be distinguished from prefibrotic myelofibrosis and chronic myeloid leukemia. We present the case of a patient who had ET and descending colon cancer since the diagnosis.

CASE REPORT

The patient, aged 70, with a personal history of acute myocardial infarction, for which a coronary stent had been implanted, was hospitalized 2 years and 5 months ago to investigate a thrombocytosis discovered in a blood count performed in ambulatory.

The investigation of the digestive tract diagnosed a descending colon cancer (which produced an axial stenosis having a length of 6 cm), and myelogram revealed the existence of a proliferation of megakaryocytes with an increased number of mature, large and even giants megakaryocytes, and rise the suspicion of an ET.

A blood sample was collected in order to determine *JAK2V617F* mutation, then the patient was operated. A segmental resection of descending colon with end-to-end transverse-sigmoid anastomosis and external drainage were performed. Histopathology confirmed the colon adenocarcinoma. Upon returning from surgery it was found that *JAK2V617F* mutation was present in heterozygous variant, important argument to support the diagnosis of ET (together with the known thrombocytosis of 1066000/mm^3 and the myelogram aspect). White blood cells and hemoglobin had normal values and the mean platelet volume was 8.9 fl.

Although radiotherapy was proposed initially, oncology committee considered that it was not necessary. Due to the presence of a thrombotic accident in the history, he had indication for cytoreductive therapy with hydroxycarbamide (500 mg/day), under which megakaryocyte proliferation was controlled (platelet count was maintained at below 400,000/mm^3). For his associated ischemic heart disease and hypertension, the patient was treated with atorvastatin 40 mg/day, aspirin 75 mg/day, metoprolol 2x25 mg/day, and enalapril 10 mg/day. He remained asymptomatic until five months ago, when he presented haematochezia stools and diffuse abdominale pain.

Colonoscopy revealed a colonic tumor and CT-scan - rectum and descending colon wall thickening and small abdominal lymph nodes. Left hemicolectomy with end-to-end colo-rectal anastomosis was performed this time.

Pathological examination revealed the presence of moderately differentiated tubular adenocarcinoma, with subserosal infiltration, and present lymphatic invasion, without metastases in the three taken lymph nodes; resection margins were without tumor involvement (stage pT3N0Mx, DUKES MAC B2). The patient returned 3 weeks after surgery for abdominal pain in the left flank, haematochezia stools, vomiting and fever. From the clinical point of view, he had signs of acute abdomen and biological - signs of inflammation, leukocytosis with elevated neutrophils, and anemia. Abdominal CT-scan showed the presence of a peritoneal fluid collection with air-water level.

The surgery evacuated a lateral-left colic abscess, but the further development was unfavorable: a fistula of colo-colonic anastomosis appeared, followed by enterorrhaphy performing at anastomosis site, and then suppression of anastomosis and installation of a left iliac anus on transverse colon. Gradually, the clinical patient's condition worsened with the deterioration of consciousness and cardiac arrest.

DISCUSSION

The patients with ET are likely to develop hemorrhagic or thrombotic events (including myocardial infarction) and progress in time towards secondary myelofibrosis and acute leukemia transformation.

We can suspect that our patient had ET when he developed acute myocardial infarction (but at that moment the disease was not detected), due to the fact that patients with ET have an increased ADP-induced platelet aggregation compared to witnesses without ET; they also have high levels of thrombin generation (TG) [1]. These explain the thrombotic events that may complicate the evolution of this disease. Other authors have also found increased TG potential in platelet-rich plasma of patients with myeloproliferative neoplasms (including of those with ET) (including of those with ET) compared to control group. Those who presented *JAK2V617F* mutation also showed the highest level of TG and platelet activation (the presence of the highest values of P-selectin on platelet surface) [2]. These patients also have an acquired thrombomodulin resistance, partly explained by the presence of circulating microparticles [3] with platelet and endothelial markers, expression of platelet and endothelial activation, which increases their risk of thrombosis [4]. In addition, the chronic inflammation present in ET predisposes to premature atherosclerosis development [5]. Coronary atherosclerosis and prothrombotic status favored, probably, the major coronary accident occurrence in the history of our patient.

It is important to make the diagnosis and treatment of ET early, in order to prevent thrombotic events. It was observed that patients treated with hydroxycarbamide had a significantly lower TG potential compared to those who did not receive such a treatment; TG potential had the lowest value in *JAK2V617F* positive patients treated with hydroxycarbamide [2]. There is information suggesting that microparticles activity (such as circulating procoagulant activity) could also be reduced with cytoreductive therapy [3].

Patients with ET have an increased risk to develop a second cancer [6]. In a recent study myelo- and lympoproliferative diseases were found to be synchronous in 6 patients (35% of them), but in other patients one disease preceded the other one a few years [7]. Such a patient with ET developed after a few years chronic lymphocytic leukaemia [8]. But the second cancer can also be a non-hematological one [9]. It is possible that our patient had (undiagnosed) ET and have developed colon cancer subsequently.

Is there any connection between these two cancers? Is is known that chronic inflammation which is present in ET can initiate a clonal evolution and a second cancer occurrence [5]. In addition, it was shown that thrombocythemia has a major negative influence on survival [9]. It was argued that platelets have a detrimental role in cancer patients evolution, by their involvement in cancer invasiveness and metastasis [9]. The "wait and watch" strategy have to be analyzed in light of these findings, in order to avoid the prognosis worsening of second cancers, due to thrombocytosis [9].

It is recommended that these patients are treated with statins and interferon alpha in order to decrease the chronic inflammation and its mentioned consequences [5].

Unfortunately, the correct treatment of our patient with hydroxycarbamide (which is today the first line of therapy for these patients) and atrovastatin (which has antithrombotic effect) was not able to avoid the colon cancer relapse. An explanation could be a possible involvement of JAK2/STAT pathway (which is activated in ET) also in colon cancer development, as was shown in some cancers [10]. It was observed that JAK2, STAT1, 3, 5A, 5B and 6 were associated with the development of colon cancer [11]. It is recognized that inflammation that predisposes to colon cancer occurrence is associated with the presence of immature myeloid cells in colon tissue [12]. Thus, we can also speculate that some leukemic stem cells came from

bone marrow, went through the torrent of blood and were placed in the large intestine, where they transformed in colon cancer-initiating cells, with *JAK2V617F* mutation present, and possibly involved in cancer pathway.

Recently, it was shown that salidroside was able to inhibit the proliferation of a colon cancer (SW1116 cells) by decreasing the activation of proteins involved in JAK2/STAT3 pathway [10].

CONCLUSION

Each thrombocytosis should be carefully investigated to discover possible causes of secondary thrombocytosis associated with ET or an ET associated with a reactive thrombocytosis. The aim of ET treatment is to prevent thrombotic or hemorrhagic events, but also chronic inflammation and genomic instability. The initiation of cytoreductive therapy in ET remains a challenge that deserves to be studied further. The unfavorable evolution of the second malignancy raises the suspicion of the involvement of activated JAK2-STAT mechanism in its pathogenesis.

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