



## EDITORIAL COMMENT

## When specialties intersect: Acute coronary syndrome as the first clinical manifestation of myeloproliferative neoplasms



### Quando as especialidades se cruzam: síndrome coronária aguda como a primeira manifestação clínica de neoplasias mieloproliferativas

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In medicine generally as well as in individual medical specialties, there is a risk that the correct diagnosis will not be reached if only the complication of a disease is taken into account, especially if this complication is serious, and not considered as part of the whole picture. All of the available data must be considered if the patient is to be properly diagnosed and treated.

Since cardiology focuses on cardiovascular diseases, cardiologists must bear in mind that what they encounter is often a complication of a more general disease. The article by Cengiz et al. published in this issue of the *Journal*<sup>1</sup> draws attention to this need, presenting a small case series of patients with myeloproliferative neoplasms (MPNs), the first manifestation of which was myocardial infarction (MI). The article highlights the need for careful assessment of blood cell count abnormalities in these patients, since appropriate hematological therapy is able to reduce their risk of thrombotic events in general and of acute coronary syndrome (ACS) in particular.

When MI occurs in a patient who does not have traditional risk factors, alternative etiologies should be investigated.<sup>2</sup> These include hypercoagulable states, coronary vasospasm, coronary inflammation, anomalous coronary arteries, coronary dissection, and embolization.<sup>3</sup>

Patients across all age groups with MPNs are reported to be at increased risk for arterial and venous thrombosis compared with matched controls, with the highest rates at and shortly after diagnosis.<sup>4</sup> MPNs are clonal disorders of hematopoiesis characterized by proliferation of one or more myeloid lines in bone marrow. The most important in clinical practice are chronic myeloid leukemia and other Philadelphia chromosome-negative chronic MPNs,<sup>5</sup> including the classic Philadelphia chromosome-negative chronic MPNs polycythemia vera (PV), essential thrombocytosis (ET) and primary myelofibrosis (PMF) in the early/prefibrotic or the overt fibrotic stage. Less frequent chronic MPNs include chronic neutrophilic leukemia, unspecified chronic eosinophilic leukemia, and unclassified chronic MPNs.

The *JAK2* V617F mutation is detected in 90-95% of patients with PV, 60% of patients with ET and 60% of patients with PMF. The presence of *JAK2* mutations was included as a major diagnostic criterion in these three entities in the World Health Organization classification in 2008 and in the revised version published in 2016.<sup>5</sup>

MPNs are associated with hypercoagulable states and thrombotic complications are more prevalent than bleeding complications.<sup>6</sup> Thrombotic occlusions occur more frequently in arteries than veins. Stroke is the most frequent presentation, followed by MI and peripheral arterial occlusion.<sup>2,3</sup>

Previous research into the pathogenesis of ACS has shown the importance of platelet thrombus formation caused by vascular endothelial damage resulting from plaque rupture.<sup>7</sup>

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JAK2 V617F-positive chronic MPNs commonly display dysfunction of integrins and adhesion molecules expressed on platelets, erythrocytes, and leukocytes.<sup>8</sup>

Venous and arterial thrombosis is the major cause of morbidity and mortality in PV and ET patients.<sup>9,10</sup> Strikingly, the thrombotic risk in these patients is dramatically higher than in patients with secondary erythrocytosis or thrombocytosis. This indicates that disease-intrinsic factors play a major role. Indeed, it has been reported that the JAK2 V617F mutation leads to abnormal function of erythrocytes and platelets.<sup>11,12</sup>

PV generally causes increased production of granulocytes, platelets and erythrocytes, particularly the latter, which leads to hyperviscosity and increased risk of thrombosis.<sup>13</sup> MI and sudden death are complications of newly diagnosed or untreated PV; they occur most often in elderly people (aged  $\geq 65$  years) with underlying coronary artery disease (CAD).<sup>13</sup> However, younger patients with PV who are free from CAD can also be affected, and sometimes the outcome is death.<sup>13</sup> In patients with PV, the main causes of mortality are MI and heart failure.<sup>14</sup>

Cytoreductive treatment of blood hyperviscosity by phlebotomy or chemotherapy and antiplatelet therapy with low-dose aspirin have dramatically reduced the incidence of thrombotic complications and substantially improved survival in PV.<sup>15</sup>

In ACS patients with ET but without a previous history, it is not easy to recognize the underlying disease, but it is essential.<sup>16</sup> Patients suffering ACS due to ET have few or no common risk factors for atherosclerosis, unlike other ACS cases. This is because the events are mainly due to thrombosis, as shown by lower plaque burden on angiography.<sup>16</sup> Most cardiologists tend to focus more on the diagnosis and treatment of CAD, especially revascularization, than on blood cell count abnormalities, resulting in a missed diagnosis of ET in patients without marked thrombocytosis. Treatment of ACS with underlying ET should consist of three steps: cytoreduction, antithrombotic therapy and revascularization.<sup>16</sup>

Combining their experience with other authors' opinions, Xiong et al.<sup>16</sup> suggest the following triad as a red flag to look for ET in ACS:

- (1) ACS with no or few CAD-related risk factors;
- (2) platelet count  $>450 \times 10^9/l$ , even if only slightly above this level;
- (3) no severe atherosclerotic narrowing found on coronary angiography, although thrombotic occlusion may be found.

Management of ET consists of antiplatelet therapy, mainly aspirin, and cytoreductive therapy that may include phlebotomy, hydroxyurea, anagrelide, interferon, and ruxolitinib, which is an inhibitor of JAK1 and JAK2.<sup>3</sup> Aspirin combined with cytoreductive therapy is considered to be highly effective in PV and ET patients.<sup>2</sup>

ACS occurring as the first manifestation of MPN is usually described in case reports. In their article, Cengiz et al.<sup>1</sup> present a small case series that draws attention to the need to be alert to the possibility of MPNs in young adults presenting with ACS, especially in the absence of atherosclerotic

coronary artery lesions. It also stresses the importance of blood cell count abnormalities and the need for early diagnosis and initiation of specific treatment, which is essential to reduce the risk of further events and of mortality and morbidity related to thrombotic complications.

## Conflicts of interest

The author has no conflicts of interest to declare.

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