# Myelo and lymphoproliferative disease: risk factors for ischemic coronary disease

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**Abstract**

The authors present a case of a 76 years old man with angina pectoris, associated with thrombocythemia, interstitial lung disease and monoclonal gammopathy of uncertain significance (MGUS).

We comment the evolution and treatment of angina pectoris, and some considerations are made about the association of those diseases in the course of angina pectoris.

Key words: angor pectoris, idiopathic thrombocythemia, interstitial lung disease, MGUS.

## Introduction

The essential characteristic of angina pectoris, in terms of pathophysiology, is the fact that the oxygen supply to the myocardium is less than is required. Atherosclerosis of the coronary arteries is by far the most common etiological factor. Occasionally however, other entities have also been involved, such as arterial spasm, thromboembolism of the coronary arteries, vasculitis and changes in coagulation and blood viscosity or platelet function, even if these are not related to atherosclerosis or myocardial mass.[1]

In this clinical case, besides the patient's age and gender there were no other evident risk factors. Nevertheless, the coexistence of essential thrombocythemia, which involves considerable hemostatic changes,[2] a restrictive, chronic lung disease, which may be a causal factor of hypoxemia, and a monoclonal gammopathy of undetermined significance (MGUS) with probable effects on viscosity and coagulation, may have significantly contributed to the genesis of ischemic heart disease in this patient.

Also of particular interest in this clinical case seems to be the coexistence of a simultaneous monoclonal proliferation of two different hematological strains, which is statistically much rarer than the occurrence of two synchronous solid neoplasms, making it unclear whether it is a disease in an ancestral "parent cell", or simply a coincidence.

## Case report

Male patient, 76 years of age, a retired salesman, born in Alentejo, residing in Sintra, admitted to our department with increasing precordial pain with fifteen days of evolution. The patient had a history of angina pectoris five years earlier, and reported the onset of an irritating cough and fatigue, several months previously. Fifteen days prior to admission, thrombophlebitis appeared in the right inner thigh.

The personal history contains no atherosclerotic risk factors. The family history contained nothing of relevance.

Objective examination: the patient was alert and cooperative, with lip cyanosis and nail clubbing, and afebrile. Blood pressure was 160/90mmHg. The pulse was arrhythmic. Heart auscultation revealed complete arrhythmia. In the pulmonary auscultation, murmurs were audible in the lower half of both hemithoraxes. Abdominal examination was normal, without hepatosplenomegaly. The presence of a fibrous line was observed, on the inner right thigh. The neurological exam and fundoscopy were normal.

The laboratory values on admission were: blood red cells 4,150,000/mm3, Hgb 11.7 g/dL, Htc 34.5%, MCV 83 fl, blood white cells 9100/mm3 (N 61%, L 29%), platelets 1,227,000/mm3, urea 10 mmol/L, creatinine 187 mmol/L, K+ 6.0 mEq/L, and Ca2+ 8.1

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mg/dL. Electrophoresis of serum proteins revealed a peak of narrow-based g-globulin (total protein 77g/L, globulins 13.8 g/L). Arterial gasometry revealed hypoxemia and hypocapnia.

Electrocardiogram revealed auricular fibrillation with a controlled ventricular rate; negative T waves in DII, DIII and AVF.

Chest radiography showed a diffuse reticular micronodular infiltrate in both lung fields.

The patient received therapy for the angina, with continuous infusion of heparin, aspirin and nitrates for five days. The patient underwent a two-dimensional echocardiogram, with normal results. The patient also underwent thallium-201 perfusion scintigraphy at rest and during exercise, which revealed the presence of ischemia in the lower wall.

As during this period a progressive increase in thrombocytosis was observed, an etiological investigation was begun, ruling out the most likely causes of secondary thrombocytosis in this patient, given the associated pulmonary condition (tuberculosis, lung neoplasm and sarcoidosis). Therefore, the following tests were performed: 1 - Mantoux test (5 mm induration), 2 - tests for BK in various samples of gastric juice - negative; 3 - CT scan of the chest that revealed a bilateral patchy ground-glass pattern with areas of fibrosis and peribronchial thickening linked to the process of pulmonary fibrosis; 4 - bronchoscopy: atrophy of the bronchial mucous membrane; 5 - bronchoalveolar lavage: total number of cells 20x104/mL; macrophages 87%; lymphocytes 12%; 2% neutrophils. 6 - study of neoplastic cells in various samples from the aspiration of negative bronchial secretions; 7 - determination of angiotensin converting enzyme and normal serum lysozyme; 8 - determination of normal urinary calcium; 9 - X-rays of the hands, normal.

Investigation of other forms of myeloproliferative disorder was initiated, performing the following tests: 1 - Peripheral blood smear: erythrocyte anisopoikilocytosis and platelet anisocytosis. 2 - Myelogram: increased megakaryocytic series; hyposegmentation of the plasma megakaryocyte core in a number higher than normal (8% of total cellularity); erythrocytic and myeloid series showed no changes. 3 - Bone biopsy: moderate increase in the number of megakaryocytes, with a slight polymorphism and predominance of large forms, forming clusters; no accentuation of the reticulin network was observed; 4 - search for Philadelphia chromosome (Ph1), negative; 5 - platelet aggregation count: decreased aggregation with collagen, epinephrine and ADP. 6 – Determination of leukocyte alkaline phosphatase 200 (N:15-100) dose.

The tests led us to make a diagnosis of essential thrombocythemia, according to the Polycythemia Vera Study Group criteria (1986).

In relation to the pulmonary condition that justified partial respiratory insufficiency, the hypothesis of pulmonary embolism was ruled out by ventilation/perfusion scintigraphy.

CAT scan of the chest was consistent with a process of interstitial fibrosis; respiratory function tests revealed a moderate restrictive pattern, marked bronchial obstruction and a decrease in lung distensibility. The patient also underwent bronchoscopy with bronchoalveolar lavage, and cytology test of the bronchial secretions, which were inconclusive in relation to the possible etiology of the pulmonary condition.

A test with gallium 67 was performed, revealing no evidence of active inflammatory process.

Serum protein immunoelectrophoresis revealed an IgG K monoclonal gammopathy (IgG 22.5 g/L, K chains 22.2 g/L) without any changes in the other immunoglobulin classes. Urine immunoelectrophoresis revealed the strong presence of Bence-Jones protein (540mg/in 24h urine). The b -2 microglobulin was high (7.7 IU/mL). Radiological examination of the skeleton was normal.

Therapy with hydroxyurea (1.5 g/day) was initiated, with normalization of the platelet count and mild myelosuppression.

The clinical condition evolved favorably without recurrence of angina pain, with platelet counts within the normal range and a dose of hydroxyurea of 1.0 g/day. A year after the onset of the symptoms, the patient suddenly died in the outpatient department and no anatomopathological examination was performed.

## Discussion

Essential thrombocythemia is a chronic myeloproliferative disorder characterized by a persistent elevation in the platelet count in the peripheral blood, and an excessive proliferation of megakaryocytes in the bone marrow.[2] Like other myeloproliferative disorders, it is a clonal disorder involving the pluripotent haematopoietic stem cell.[3,4,5]

Of the myeloproliferative disorders, essential thrombocythemia is the one that is the most difficult to diagnose as unlike the others, it has no pathogno-

**TABLE I**

**Diagnostic criteria – essential thrombocythemia**

1) Platelet count > 600000/mm$^3$
2) Hemoglobin <13g/dL or normal erythrocyte mass (H<36 mL/kg and M<32 mL/kg)
3) Presence of iron in the bone marrow or lack of response to therapeutic trial of iron
4) Absence of Philadelphia chromosome
5) Bone marrow fibrosis absent or in less than 1/3 of the biopsy site without splenomegaly or leukoerythroblastic reaction
6) Absence of reactive thrombocytosis

**TABLE II**

**Causes of reactive thrombocytoses**

1) Iron deficiency
2) Chronic inflammatory diseases
   a) Wegener's granulomatosis
   b) Inflammatory bowel diseases
   c) Rheumatoid arthritis
   d) Polyarteritis nodosa
3) Chronic infections
   a) bacterial
   b) fungal
   c) tuberculosis
4) Drugs
   a) Vinca alkaloids
   b) epinephrine
5) Post-splenectomy
6) Neoplasms
   a) lymphomas
   b) lung and colon carcinoma
7) Rebound thrombocytosis
   a) post-treatment of ITP
   b) post-treatment of pernicious anemia
   c) post-treatment with myelosuppressive agents
   d) acute blood loss
8) Myelodysplastic syndromes
   a) 5q-syndrome
   b) sideroblastic anemia
   c) hemolytic anemia

monic markers, and is therefore considered a diagnosis of exclusion. To overcome this inconvenience, the Polycythemia Study Group proposed, in 1982, six criteria for diagnosing essential thrombocythemia (*Table 1*).[4]

Ruling out reactive thrombocytosis is one of the most important criteria in the diagnosis of essential thrombocythemia. The thrombocytosis may be associated with various diseases (*Table 2*).[4]

In the clinical context of our patient, the investigation was directed towards ruling out the most likely causes of reactive thrombocytosis (tuberculosis, lung neoplasm and sarcoidosis).

Essential thrombocythemia is considered an indolent disorder with a normal life expectancy.[4] The main clinical manifestations are characterized by hemorrhagic and thromboembolic phenomena, and there appears to be no relation between these and platelet count. The sites of bleeding reflect a defect in primary haemostasis, and tend to involve the mucocutaneous surfaces. The thrombotic episodes may involve either the veins or arteries. Arterial occlusions tend to occur mainly in the microcirculation, although large arteries may also be involved, as is the case with the coronary region.[2,3,4,6]

Thrombocythemia is an important vascular risk factor, and it is likely that thromboembolic events in patients with essential thrombocythemia occur regardless of the presence of atherosclerotic risk factors.[2]

Studies of platelet function have shown multiple changes, and are important in differentiating between reactive and myeloproliferative thrombocytosis.[4] The most characteristic defect is the total absence of aggregation with epinephrine, which appears to be due to a total loss of alpha-adrenergic receptors on the platelet surface.[2,7] On the other hand, several authors have reported hyper-aggregation of platelets "in vitro" and spontaneous aggregation, which could be related to a greater predisposition for the development of thromboembolic events.[7] More recently, it has been possible to study platelet activation "in vivo" by demonstrating high levels of beta-thromboglobulin in the plasma.[4]

Recent studies have shown that thrombotic events in patients with essential thrombocythemia may be related to a decrease in platelet levels of the plasminogen activator inhibitor (PAI-1)[8]. A hypofibrinolytic

condition in these patients may be an additional factor that could be useful for predicting thromboembolic events.[9]

The patient was admitted with symptoms of ischemic heart disease (increasing angina pectoris), supported by electrocardiogram at rest and thallium-210 perfusion scintigraphy at rest and during exercise. The patient had also had an episode of venous thrombosis a few days before admission, probably as part of the essential thrombocythemia.

The absence of atherosclerotic risk factors other than age and gender leads us to consider the important role of thrombocytopenia in this clinical setting.

Ischemic heart disease is one of the main heart complications in patients with essential thrombocythemia, as demonstrated by various studies.[3,10]

The treatment of patients with essential thrombocythemia is very controversial. It seems clear, however, that patients with thrombotic or hemorrhagic complications should receive treatment to reduce the platelet count.[4,5]

Hydroxyurea appears to be the drug of choice, given its effectiveness and low toxicity.[5] a-interferon has proven to be effective in controlling thrombocytosis associated with myeloproliferative diseases, suppressing megakaryopoiesis and decreasing the platelet half-life.[11,12]

In this patient, we decided to begin therapy with hydroxyurea, not only for its proven effectiveness, but also, subjectively, because of the bad experience the authors had had with a-interferon in a patient with essential thrombocythemia who, in addition to myalgias and malaise, had a serious toxidermia that led to discontinuation of the therapy.[13]

Monoclonal gammopathy of undetermined significance (MGUS) is an entity characterized by the presence of a peak monoclonal protein (M component) in the absence of multiple myeloma, Waldenstrom's macroglobulinaemia, amyloidosis or other related pathologies. MGUS is characterized by a serum concentration of the M component below 3g/dL, absence or low concentration of Bence-Jones proteinuria in the urine, absence of lytic bone lesions, hypercalcemia and renal insufficiency; perhaps the most important criterion is the stability of the M component.[14]

Another important aspect is the percentage and morphology of bone-marrow plasma cells. The presence of plasma cells without dysmorphic features and at a percentage lower than 10% is highly suggestive of a benign monoclonal gammopathy.[15] The prevalence of MGUS is 3% in people aged over 70 years.[16]

Monoclonal gammopathy may be associated with other pathologies, including lymphoproliferative diseases, leukemia, sensory-motor polyneuropathy of unknown etiology, and skin diseases whose prototype includes lichen myxedematosus.[17]

The patient in this clinical case had signs of monoclonal gammopathy of undetermined significance (M component 2.2 g/dL, 8% bone-marrow plasma cells, absence of anemia, hypercalcemia, and lytic bone lesions).

The presence of Bence-Jones proteinuria and a high concentration of 2 microglobulin are two warning signs of a possible evolution to a malignant monoclonal gammopathy. In a prospective study conducted by the Mayo Clinic, 241 patients with benign monoclonal gammopathy were followed for 20 years, and it was found that 24.5% of these patients developed multiple myeloma, Waldenstrom's macroglobulinaemia, amyloidosis or other related disease, and only 19% remained with a benign condition.[16]

The existence of monoclonal proliferation of two different haematopoietic lineages (megakaryocytic and lymphocytic) should be noted in this patient. This association may suggest an alteration in the haematopoietic stem cells, or it may be just a coincidence, which seems the most likely option.[18]

Interstitial lung diseases are a heterogeneous group of nosological entities with a common chronic inflammation involving all the components of the alveolar wall, which can progress to the appearance of excessive connective tissue with distortion of the lung structure.[19,20]

Interstitial lung diseases can be etiologically classified as occupational, drug-induced, associated with connective tissue diseases, the result of a primary lung disease or idiopathic. The primary lung diseases include sarcoidosis, hypersensitivity pneumonitis, eosinophilic granuloma of the lung, lymphangitic carcinomatosis, lymphangioleiomyomatosis and alveolar proteinosis. [20] Approximately 30-40% of all cases are idiopathic, the majority being attributed to idiopathic pulmonary fibrosis or bronchiolitis obliterans.[20]

Clinically, patients have dyspnea of insidious onset and progressive in nature, which may be accompanied by a dry, irritating cough. Objectively, the existence of cyanosis and nail clubbing is common, as well as the presence of lung murmurs on pulmonary aus-

cultation. The most common radiological change is a diffuse reticulo-micronodular pattern, although the most pathognomonic aspect that guarantees the existence of interstitial fibrosis is honeycomb lung.[19]

The main ventilatory alteration is a restrictive syndrome often associated with an obstructive component of the small airways. As a result of these changes, the existence of low lung volumes, decreased capacity of the lung to diffuse carbon monoxide, and the presence of hypoxemia and hypocapnia, are common.[19]

Bronchoalveolar lavage has brought important findings to the study of interstitial lung diseases. The interest in this technique is based on the fact that the cellular and non-cellular components in the alveolar surface mirror the immune and inflammatory processes that take place in the interstitium.[20]

The bronchoalveolar lavage in our patient showed a slightly elevated percentage of neutrophils for a non-smoker, which is characteristic of idiopathic pulmonary fibrosis.

In this patient, sarcoidosis was the main hypothesis, which would not only explain the pulmonary symptoms, but also a reactive thrombocytosis. The study performed and already described led us to rule out this hypothesis, leaving us with the hypothesis of idiopathic pulmonary fibrosis as the most likely one, especially in view of the patient's age group and the bronchoalveolar lavage. The gallium 67 scintigraphy ruled out the existence of an active inflammatory process.

## Conclusions

1) Despite the patient's age and gender, the thrombocytopenia played a definite role in aggravating the ischemic heart disease, associated with hypoxemia resulting from the interstitial lung disease.
2) MGUS appears in around 3% of people aged over 70 years. It does not seem to be a condition of clinical or laboratory hyperviscosity, although it has not been proven that the minimal dysproteinaemia do not interfere with coagulation, and they may have aggravated the patient's ischemic heart disease.
3) Interstitial lung disease does not seem to be a causal factor of thrombocytosis, but may lead to continuous immune stimulation to the onset of MGUS.
4) The monoclonal proliferation of two different haematopoietic lineages (megakaryocytic and lymphocytic) appears to be a coincidence, and an alteration in haematopoietic stem cells cannot be ruled out. ■

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